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MELANIN

I. ITS MOBILIZATION AND EXCRETION IN NORMAL AND IN PATHOLOGIC CONDITIONS

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The numerous problems concerning normal and pathologic endogenous pigmentation offer difficulties in their solution derived from the fact that the absolute identification of a pigment unaltered by extravital chemical reactions is rarely possible. The gradation of colors through the various shades of yellow and brown to black includes substances which often have a certain basic molecular similarity but which, nevertheless, may be the result of fundamentally different cellular activities. Undoubtedly too much importance has been given to the presence of stainable iron or lipoid in differentiating microscopically one colored body from another. Progress in this difficult field of study will necessarily be as slow as improvement in laboratory methods, especially in microchemical technic.

The distribution of hemosiderin, it is assumed, can be determined best by the demonstration in granules of iron through the use of the prussian blue test and its modifications and by the reaction of iron with ammonium sulphide. We shall allow, for the sake of argument, that iron in this form is indicative of hemosiderin. When, however, the iron is identified only after the maceration or digestion of tissues, and then usually in minute quantities and by highly refined chemical methods, it cannot be accepted that the pigment is necessarily hemosiderin.

One of the pigments which occurs in unicellular organisms as well as in Mammalia is called melanin. Its normal distribution in man, according to Bloch,[1] is confined to the skin, the pigment layer of the retina, the ciliary body and the choroid, except for its occurrence in certain parts of the central nervous system. Melanin is difficult to isolate since it does not crystallize and is soluble with difficulty in fluids

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1. Bloch, B.: Am. J. M. Sc. **177**:609, 1929.

which offer the least possibility of altering its complex molecule. From this fact alone it seems unwise to limit its normal presence to the skin and the eye, since other morphologically similar pigments are found elsewhere in the body which, when deprived of loosely held sulphur or iron, for instance, may prove to be members of this group of endogenous pigments.

Since melanin is formed normally within the body by the melanoblasts and is transported by the melanophores, a certain amount of the pigment must constantly be disposed of in some way following the obsolescence or disintegration of the cells containing it. What is the fate of this pigment? Some of it undoubtedly escapes into the intestinal canal. Melanosis of the colon is encountered in chronically constipated persons, the pigment being found in phagocytes in the mucosa. The mucosa of the appendix frequently contains melanin. Does the kidney play a part in the excretion? In a note on melanins, Hawk [2] stated:

> These pigments never occur normally in the urine, but are present under certain pathological conditions. . . . In many instances, without doubt, urines rich in indican have been wrongly taken as diagnostic proof of melanuria. . . . The pigment melanin is sometimes mistaken for indigo and melanogen for indican. . . . In rare cases melanin is found in urinary sediment in the form of fine amorphous granules.

The kidney of the adult often contains a yellowish-brown pigment in the form of coarse granules in the epithelium of the collecting tubules and Henle's loops and, less frequently, in the convoluted tubules. This pigment gives a negative reaction for iron but appears to contain a lipoid from its reaction with fat stains and osmic acid. Since the Negro produces normally the greatest amount of melanin found in man, it should follow that he would show the greatest normal excretion of the pigment.

This study is an outgrowth of a more comprehensive survey of the significance of melanin in normal and in pathologic cells. A fundamental difficulty lies, of course, in the inadequacy of the methods of identifying melanin. Its argyrophilia, however, offers an approach which Foot [3] has utilized in his work with benign and malignant melanotic tumors. Using his method, with a slight modification, we have studied the distribution of melanin in the normal kidneys of adult Negroes, in patients with Addison's disease, in Negroes with malignant melanoma with generalized metastases, in blonde and brunette white persons and in more than four hundred white mice, each of which had a melanoma derived from one originally discovered by Harding and Passey [4] at Guy's Hospital in 1915 and obtained by us from Sugiura of the Memorial

2. Hawk, P. B., and Bergeim, O.: Practical Physiological Chemistry, ed. 10, Philadelphia, P. Blakiston's Son Co., 1931, p. 776.

3. Foot, N. C.: Am. J. Path. **7**:619, 1931.

4. Harding, H. E., and Passey, R. D.: J. Path. & Bact. **33**:417, 1930.

Hospital, New York. The technic of Foot is only one of many technics based on the use of silver nitrate, but it is very satisfactory for the demonstration of melanin as well as of reticulum.

Many kinds of cells or their inclusions or processes may be impregnated by silver salts under certain conditions; hence it is advisable always to state by what method their argyrophilia is demonstrated. The term argyrophilia is a bit vague, as Nageotte of Paris stated to Laidlaw,[5] but what it should mean is the relative degree of affinity for silver salts displayed by one type of substance as compared with another under similar conditions. We have had much experience with Foot's

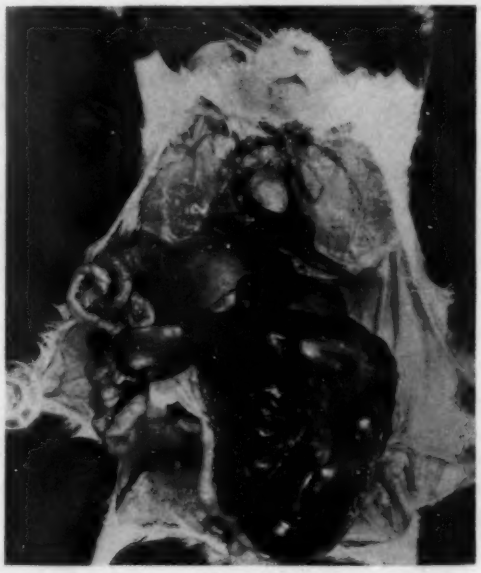

Fig. 1.—A white mouse with a large intraperitoneal Harding-Passey melanoma resulting from the intraperitoneal inoculation of an emulsion of mouse melanoma two hundred and twenty-four days previously. There are a few small metastases in the liver and the lungs. The kidneys showed marked melanosis.

silver methods, and in order that a comparison of results might be based on a uniform technic, his bromuration procedure has been used, largely to the exclusion of other variations.

The isolation of melanin in a pure state is apparently impossible at present because of its relative insolubility in vitro without the aid of a strong alkali or acid. It must be soluble in certain body fluids or it possibly exists as a colloidal suspension, because either it or its precursor, melanogen, is present in the urine in many cases of melanoma, and,

5. Laidlaw, G. F.: Personal communication to the authors.

while it is phagocytosed by various cells, it has never, to our knowledge, been detected in particulate form in the cells of the circulating blood. While melanin has apparently not been seen in circulating leukocytes, Davis [6] has noted its ingestion by white blood cells and also by cells of the renal tubules and entodermal cells of the intestine in tissue cultures. Since melanin is a constant component of many cells of the body, it follows that the pigment must be disposed of in some way when melanophores die; the ordinary catabolic processes probably destroy but a small amount of it. Odiorne [7] has shown that a certain amount of melanin escapes from the body of the killifish (Fundulus heteroclitus) in the desquamation of epithelium from the pigmented spots. This method undoubtedly accounts for the loss of much melanin from the integument in all pigmented species.

The accurate identification of melanin either in vivo or in vitro is not possible for the reasons already given. Yet there is much literature on melanin, and dogmatic statements have been made and probably will continue to be made concerning this substance, at least until a microchemical test has been devised which is above criticism. This will be possible only after the chemical composition of melanin is definitely known. As things stand, much of the proof that a given pigment is melanin is circumstantial. First, it may be found in cells which give a positive dioxyphenylalanine reaction, that is, cells capable of oxidizing l-3-4 dioxyphenylanaline to a pigment indistinguishable from melanin. These cells are regarded as melanoblasts in contradistinction to cells which can only phagocytose melanin but cannot manufacture it. This conception hinges on the absolute specificity of Bloch's dopa reaction as indicating melanoblasts only. There are still several weaknesses to be remedied in the application of this reaction before it can be approved in this degree, but the outlook is good for final acceptance.

Second, melanin may be seen as a dark brown granular pigment in the tumor arising from the cells of a pigmented nevus, whether or not the dioxyphenylalanine reaction is studied; this pigment is negative for stainable iron.

Third, it may be found in fibroblasts, monocytes and reticuloendothelial cells adjoining an area of pathologic pigmentation, for instance, a melanoma, or in the skin in a case of excessive melanosis, such as Addison's disease.

The use of frozen sections has seen wide application in recent years in the rapid diagnosis of tissue, in the study of the distribution of fats and lipoids and in the demonstration of nerve fibrils and reticulum. It has long been known that melanin is capable of reducing silver salts,

6. Davis, D. T.: Bull. Johns Hopkins Hosp. **32**:240, 1921.
7. Odiorne, J. M.: Proc. Nat. Acad. Sc. **19**:329, 1933.

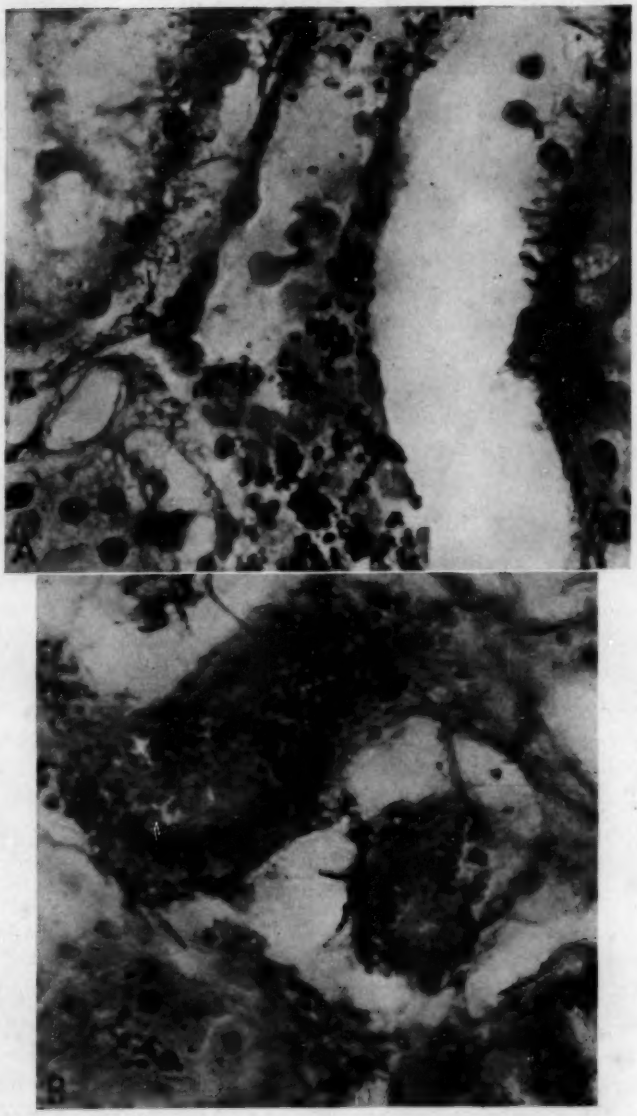

Fig. 2.—*A*, renal tubules in the kidney in Addison's disease. Melanin granules are seen in the epithelial cells and in the lumen. *B*, renal tubules in a mouse with a subcutaneous melanoma one hundred and seventy-nine days old. The melanin granules are somewhat scattered through the cytoplasm, but tend to be grouped in the midzone. Foot's silver-bromuration method.

and with the impetus given to the study of the nervous origin of pigmented nevi by Masson a renewed interest in the argyrophilia of melanin has been manifest in the most recent studies of the melanomas. However, until the identity of all the granules blackened by silver which are found in cells fixed in a solution of formaldehyde is determined, there will continue to be skepticism in regard to the conclusions drawn from the use of this method. At present it is necessary to consider all the circumstances surrounding the presence of the pigment in question, and in our study we have tried so to do. Our conclusions are based on the consideration mentioned, and it is hoped they do not seem too dogmatic when viewed in that light.

In cases of pathologic increase of melanin in the adult human being with Addison's disease or melanomatosis, the kidneys contained much yellowish-brown or deeper brown pigment in the epithelium of Henle's loops and in many collecting tubules, as well as in the reticulo-endothelial cells of the liver, spleen and lymph nodes. These pigmented granules were present in fresh unstained frozen sections, in preparations fixed in a 10 per cent solution of formaldehyde and in Zenker's fluid embedded in paraffin and stained with hematoxylin and eosin or with eosin and methylthionine chloride, U. S. P. (methylene blue). The alcohol and chloroform removed any carotene present, since it is soluble in these fluids. Other lipoids and fats were similarly extracted, leaving only a pigmented residue which was still capable of reducing silver nitrate and of being bleached by hydrogen dioxide, and the identity of which we have sought to establish.

In the renal tubules the pigment is usually found in the peripheral portion of the epithelial cell in small dustlike granules or larger agminate masses; the color varies from dirty yellow to brown, depending on the amount of pigment present. This pigment is usually called "lipochrome" but has not been regarded as melanin, so far as we are aware. Yet it occurs in large amounts in many patients with pathologic melanosis, in elderly brunettes and in constipated Negroes. It differs in no essential respect from the pigment in the mucosa of the colon in melanosis coli. It is strongly silver positive. The pigment is found in the lumen of the tubules, either in desquamated epithelium or free, having possibly been discharged from the cells or precipitated from its solution in the fluid in the tubules. It is often found in renal casts in the same manner as hemosiderin is found in hemochromatosis or pernicious anemia. In one of our cases of Addison's disease, proved by necropsy, strongly silver-positive, yellowish-brown granules were demonstrated before death in renal casts from the urinary sediment (fig. 3 *A*), and the kidneys were found to contain much pigment in the locations already noted. Similar deposits of the pigment were encountered in the kidneys of several patients with malignant melanomatosis.

In our study of the organs of white mice harboring the transplantable Harding-Passey melanoma, melanosis of the intestines was never seen. Melanosis coli is found in man only in extreme constipation. In these mice with tumors of large size, i. e., 1.5 cm. and larger, renal

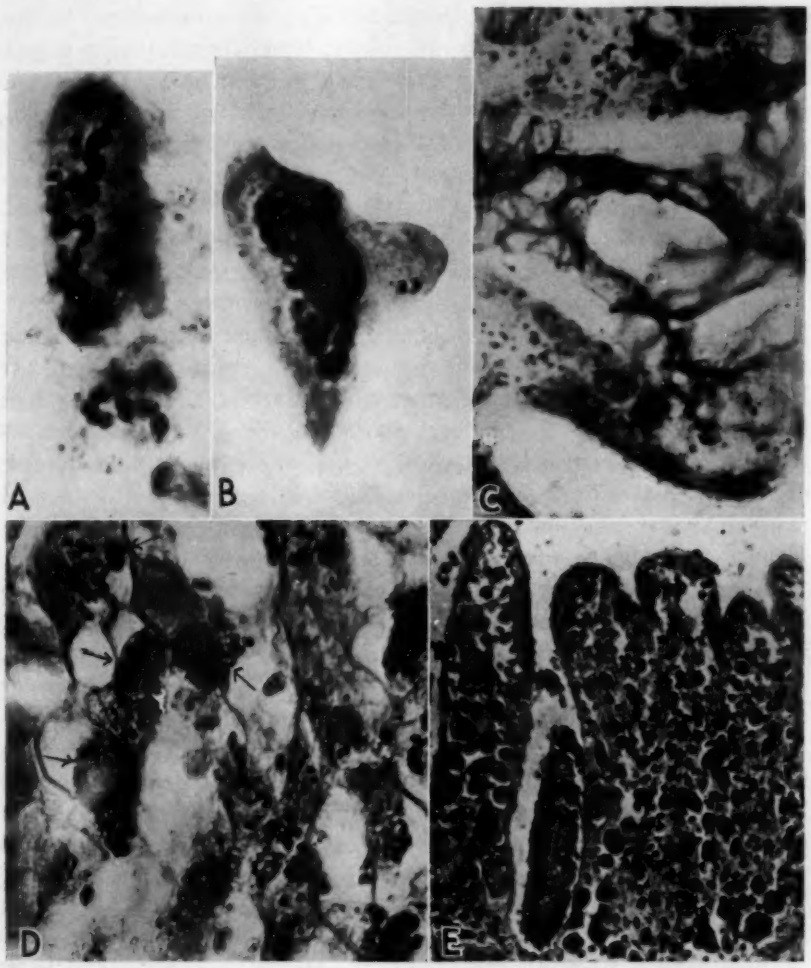

Fig. 3.—*A*, a pigmented renal cast in the urinary sediment of a patient with Addison's disease. *B*, a pigmented epithelial cell in the urinary sediment of a patient suffering from generalized melanosis with diffuse myelomatosis. *C*, renal tubules in a Negress with melanomatosis. Melanin granules are seen in the epithelium and in the tubular casts. *D*, section of the suprarenal gland of an elderly white man. Melanin granules are abundant in the cells of the medulla on the right. The arrows indicate the cells of the zona reticularis containing melanin. *E*, melanosis coli. The pigment is contained in phagocytes in the mucosa.

melanosis was encountered in a high percentage. The animals were fed the same diet as the controls, which never showed any pigmentation of the kidneys. This renal pigment is not soluble in lipoid solvents, and its ability to reduce silver is lessened slightly when it has been previously immersed in chloroform and alcohol in the process of dehydration for embedding in paraffin. Dyson [8] noted that a pigment normally of lighter color resulted from employing the solvents used for preparing tissues for paraffin, and he asked if there were two different forms of melanin. Melanin, he stated, is included in the protein part of an excretion of the cell nucleus, a bluish granule of lipoid and protein being the precursor of the pigment. The chemistry of melanin will not be discussed in extenso in this paper, but because of its reaction with fat stains and lipoid solvents we believe that the melanin molecule often links itself loosely with a lipoid complex.

Wells [9] stated that melanuria is not ordinarily observed unless there is extensive development of melanotic tumors, and that it is seen in only about 20 per cent of the cases of melanosarcoma, chiefly when the liver is extensively involved. Formerly the excretion of true melanin or melanogen was supposed to be diagnostic of the presence of melanosarcoma, but melanuria has been observed in persons without tumors of this type and with no other evident source of the pigment. In several cases there was intestinal obstruction, from which the precursors of the pigment may have resulted through the disintegration of protein.

Schreyer [10] noted in the renal epithelium a pigment resembling the lipofuscins, which increases with age and which is not related to the urinary pigments. Brahm and Schmidtmann,[11] on the other hand, expressed the belief that lipofuscin is physically and chemically similar to melanin and that it is probably absorbed or dissolved by lipins.

Risak and Asperger,[12] in studying the appearance of melanin reactions in human urine, found that after intense solar irradiation a positive Thormählen reaction developed in the urine of a normally pigmented person, a phenomenon not previously observed in irradiated and tanned persons. In persons poor in pigment this reaction was not observed.

The kidney of the adult Negro frequently contains in Henle's loops and in the collecting tubules granular pigment, which, so far as we can determine, is melanin. There is an increase in renal pigment in the constipated Negro. In white adults, especially in brunettes, who have

8. Dyson, W.: J. Path. & Bact. **15**:298, 1910.

9. Wells, H. G.: Chemical Pathology, ed. 5, Philadelphia, W. B. Saunders Company, 1926, p. 530.

10. Schreyer, H.: Frankfurt. Ztschr. f. Path. **15**:333, 1914.

11. Brahm, B., and Schmidtmann, M.: Virchows Arch. f. path. Anat. **239**:488, 1922.

12. Risak, E., and Asperger, H.: Klin. Wchnschr. **11**:154, 1932.

died of severe wasting disease, i. e., diseases accompanied by widespread destruction or atrophy and desquamation of cells (including, of course, the many tissues which either make or contain melanotic pigment), the kidneys usually show melanosis. In melanosis coli the pigment in phagocytes in the colonic mucosa seems to be true melanin and occurs only in very constipated people. As has been stated before, the kidneys of mice with subcutaneous or intraperitoneal melanomas contain much melanin. The intestinal mucosa is free from melanin, but if one could produce chronic constipation in mice with this condition melanosis coli might possibly ensue. Recently Bockus, Willard and Bank [13] suggested that melanosis coli is the result of the use of anthracene laxatives, such as cascara sagrada, but if this were true melanosis coli should be more frequent in view of the wide use of these laxatives. However, little is known about the exact mechanism of melanin formation, and in the intestines such synthesis may be possible, given the proper materials and conditions.

The pigment present in the zona reticularis of the human suprarenal gland has been known by various names; usually it has been dismissed as lipochrome. However, since it is still present after dehydration in alcohol and chloroform it must be something else, as carotene and xanthophyll, the principal lipochromes, are soluble in fat solvents. The pigment which normally gives a yellow color to the entire cortex of the suprarenal gland in young people probably belongs in the category of lipochromes, but the pigment in the zona reticularis of the suprarenal gland in old people, which gives a brown to black color to this layer, is not soluble in lipoid solvents and stains an intense black with silver nitrate. It behaves, then, more like melanin than like any other pigment. In our experience, the cells of the zona reticularis have always given a negative dioxyphenylalanine reaction. Laidlaw [14] has confirmed this finding. If the pigment is melanin, where does it come from? The epithelial cells of the suprarenal gland are definitely not melanoblasts. Melanin is most likely to be found in the vicinity of melanin-forming cells. The cells of the suprarenal medulla are of sympathetic origin; in other words, they arise in the neuro-ectoderm where all melanoblasts should come from, if the neurogenic origin of melanomas is correct. We have studied the suprarenal gland in many patients of various ages and have found that the granular pigment of the cells of the medulla is not soluble in fat solvents and is very silver positive. Connor regards this pigment as melanin and so do we. In figure 3 *D*, depicting a frozen section of the suprarenal gland of an old person who died of pneumonia, which was treated by Foot's silver-bromuration method, there is present

13. Bockus, H. L.; Willard, J. H., and Bank, J.: J. A. M. A. **101**:1, 1933.

14. Laidlaw, G. F.: Personal communication to the authors.

an abundance of melanin granules in the cells of the medulla. Granules of similar appearance are present in the contiguous cells of the zona reticularis, the pigment becoming less abundant the farther the cells are from the medulla. With higher powers of the microscope there even appears to be an extrusion of melanin granules by the medullary cells. The granules seem to be taken up by the cortical epithelium of the zona reticularis. These epithelial cells of the suprarenal cortex, then, act like melanophores and hence can be added to the group of cells which can carry melanin but cannot manufacture it. The list includes macrophages, endothelial cells and fibroblasts. This explanation of the origin of the melanin in the suprarenal gland harmonizes with the Soldan-Masson theory of the origin of melanotic tumors and makes it seem logical to believe that melanin, wherever it is found, is always of neuroectodermal origin.

SUMMARY

The normal distribution of melanin is confined to the skin, the pigment layer of the retina, the ciliary body, the choroid, certain parts of the central nervous system and the medulla and zona reticularis of the suprarenal gland.

While melanin is soluble in vitro only in strong alkali or acid, it must be soluble or in colloidal suspension in the body fluids, because it or its precursor, melanogen, colors the urine in many cases of melanoma. The pigment has probably rarely, if ever, been detected in particulate form in the leukocytes of the blood.

The mobilization of melanin from areas of normally or pathologically pigmented cells and the paths of its excretion from the body have been studied in aged blondes and brunettes, in adult Negroes, in patients with Addison's disease, in those with melanoma and in more than four hundred white mice each of which had the transplantable Harding-Passey mouse melanoma.

In Addison's disease and melanomatosis the kidneys contained much melanin in Henle's loops and in the collecting tubules, as did the reticuloendothelial cells of the liver, spleen and lymph nodes. Melanin granules were often present in renal casts, and one diagnosis of Addison's disease was made ante mortem partly on the basis of such a finding. The kidneys of old people, especially brunettes, and of constipated adult Negroes, who died of severe wasting disease showed similar findings. In melanosis coli the pigment in the phagocytes in the colonic mucosa seems to be true melanin and occurs only in very constipated people. The paths of excretion of melanin appear to be, then, from the skin by desquamation, through the intestinal tract and through the kidneys. The ingestion of melanin in foods and the synthesis of melanin in the intestines may account for much of the pigment in melanosis coli.

The pigment of the zona reticularis of the suprarenal gland appears to be melanin, and it is suggested that the pigment is absorbed from the neurogenic cells of the contiguous suprarenal medulla, thus adding the epithelial cells of the suprarenal cortex to the list of possible melanophores. This explanation of the origin of melanin in the suprarenal gland is in harmony with the Soldan-Masson theory of the origin of melanotic tumors and suggests that melanin, wherever it is encountered, is always of neuro-ectodermal origin.

EXPERIMENTAL EDEMA

FURTHER EXPERIMENTS ON THE TYPE OF EDEMA PRODUCED BY A DIET LOW IN PROTEIN

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Dr. Egloff and I have described [1] a method of producing hypoproteinemia and edema in a dog by feeding a diet with a low protein content. We have repeated this experiment on four adult dogs, and were able to produce hypoproteinemia of the same degree found in the first dog, but only two of the four animals became edematous when salt and water were forced by gavage. We again found an excess of fat in the renal tubules of the animals. The amount of fat in the animals that had edema and those that had hypoproteinemia without edema was quite similar, which doubtless is proof that the edema itself has little to do with the fatty deposits.

There has been a suggestion that these lesions are accidental findings (Leiter [2]). We have added control studies, lacking in the first paper, which make more convincing the evidence that the fat changes are actually a result of the experiment and not changes found in most dogs used in the laboratory. In the first place, we examined sections of the kidney from eighteen dogs used in various experiments in the laboratory which we were sure did not influence the kidneys. These sections uniformly showed little or no fat in the renal tubules. Also we fed two dogs a high fat but normal protein diet, and these dogs showed very little fat in the renal tubules.

We have been unable to prove that the fatty changes in the renal tubules were the result of protein starvation and low plasma proteins per se, for we could not show that the anemia which invariably appears in these experiments was not a potent factor in the deposition of this fat. However, Dr. George H. Whipple of Rochester, N. Y., sent us sections stained for fat from four dogs which had been kept anemic for more than a year, and only one of these showed an excess of fat in the convoluted tubules. He did not study the plasma proteins, so it is possible that this one animal had hypoproteinemia. Neither Dr. Whipple nor we are willing to admit this as positive evidence. Further experiments are in progress to control this factor.

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1. Shelburne, S. A., and Egloff, W. C.: Arch. Int. Med. **48**:51, 1931.
2. Leiter, Louis: Arch. Int. Med. **48**:1, 1931.

Therefore, we are still unable to convince ourselves that there is a definite relation between the fatty changes and the similar deposits in the convoluted tubules of patients with the nephrotic syndrome. As contrary evidence, we have been able to show that the renal fat in all of our dogs was not doubly refractile. This is of importance, as Lubarsch [3] has shown that this type of fat is characteristic of the nephrotic types of renal disease. Therefore, we report this as an interesting finding that may in the future throw some light on the complex subject of fat metabolism.

METHODS AND FURTHER COMMENTS

Four adult female dogs, weighing from 15 to 18 Kg., were selected for feedings low in protein. They were fed a normal Cargill synthetic diet and then placed on a diet low in protein. We tried Cargill's diet

TABLE 1.—*Diet A*

Constituents	Grams	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.
Lactose	75	0	0	75.0
Butter	50	0.5	42.0	
Cod liver oil	30	...	30.0	
Turnip	100	1.3	0.2	8.1
Potato	100	2.2	0.2	18.4
Bone ash	10	0	0	0
Salt mixture	2	0	0	0
Total	367	4.0	72.4	101.5

Yeast concentrate, 20 Gm. added each week

Total caloric value, 1,078 (from 60 to 70 calories per kilogram for one dog)

low in protein (synthetic), but after a short time the dogs refused this food, so we had to return to a vegetable diet similar to that used in our first experiments, but with the addition of a yeast concentrate, bone ash and a salt mixture (Cargill).

Two other dogs, 5 and 6, were placed on a diet with the same fat content, but with an adequate amount of protein. These animals were considered as proper controls on the factor of the increased fat in the diet affecting the amount of lipoid in the renal tubules.

We were able to produce edema in dogs 1 and 3 after the plasma protein fell below 4 Gm. per hundred cubic centimeters, with the albumin below 2 Gm. It is interesting to note that although very low plasma protein levels were reached in dogs 2 and 4, there was never a time when the total plasma protein was below 4 Gm. and the plasma albumin was below 2 Gm. We were unable to precipitate edema in these

3. Lubarsch, O., in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1925, vol. 6, p. 525.

animals in spite of forcing large amounts of salt and water. In summary of our total experience with this type of edema in dogs, we may say that these figures probably represent critical levels of plasma protein for the formation of edema. Of course, this is much lower than the critical levels in man.

We again noticed marked anemia in these animals after prolonged low protein feeding. We attempted to run a control on the part played by this factor in causing the fatty changes in the kidneys by removing

TABLE 2.—*Results in the Case of Dog 1*

Date	Weight, Kg.	Hematocrit, per Cent	Total Plasma Protein, Gm.	Plasma Albumin, Gm.	Plasma Globulin, Gm.	Fatty Acids, Gm.	Cholesterol, Gm.	Serum Phosphorus, Mg.	Blood Urea Nitrogen, Mg.	Diet*	Comment
12/22/30	18.4	....	...	...	...	.....	.....	...	..	N	
1/ 1/31	19.0	51.0	7.3	5.1	2.2	0.390	0.140	2.3	16	LP	
1/23/31	17.2	42.0	5.5	3.5	2.0	.....	.....	...	..	LP	
2/ 2/31	15.8	....	...	...	...	.....	.....	...	..	A	
3/ 2/31	14.4	43.5	5.1	2.7	2.4	0.340	0.187	...	..	A	
3/27/31	13.2	36.0	4.6	2.1	2.5	0.410	0.215	...	..	A	
4/25/31	11.2	36.0	4.1	2.8	1.3	0.350	0.130	...	..	A	
5/20/31	11.2	36.0	3.7	2.3	1.4	.....	.....	...	4	A	
5/22/31	11.2	....	...	...	...	.....	.....	...	..	A	1,000 cc. of 1 per cent solution of sodium chloride for 2 days
5/26/31	12.9	33.0	3.6	2.0	1.6	.....	.....	2.3	..	A	Edema
5/27/31	12.9	....	...	...	...	.....	.....	...	..	M	Left nephrectomy; edema; transfusion of 450 cc. of blood
5/29/31	13.1	23.0	3.6	2.0	1.6	.....	0.217	...	10	M	Edema
6/ 3/31	11.5	33.0	5.8	2.8	3.0	.....	0.240	...	8	M	No edema
6/13/31	13.4	32.0	6.1	3.2	2.9	.....	.....	...	..	M	250 cc. of whole blood withdrawn
7/ 3/31	12.8	31.0	4.2	...	...	0.682	0.172	...	18	M	250 cc. of whole blood withdrawn
7/15/31	12.8	24.0	3.7	...	...	0.607	0.163	...	14	M	340 cc. of whole blood withdrawn
7/18/31	12.8	24.0	3.8	...	...	.....	.....	...	..	M	Autopsy

* In this and the succeeding tables, under diet, N indicates the normal Cargill diet (synthetic); LP, the low protein Cargill diet (synthetic); A, the low protein diet (vegetable), and M, the milk (1,000 cc. daily) and meat (about 200 Gm. daily) diet.

one kidney after the plasma proteins had fallen to the edema level, allowing the protein levels to rise by feeding meat and milk, but maintaining severe anemia by bleeding, and then comparing the amount of fat in the two kidneys. Unfortunately the bleeding, or a failure to eat all of the food, resulted in the maintenance of the low plasma protein levels, and so this approach to the problem failed (tables 2 and 3).

All the kidney tissues were fixed in both formaldehyde and Zenker's fluid. Sections were stained with hematoxylin and eosin and for fat with nile blue sulphate and sudan III. An unstained section of formaldehyde-fixed tissue was examined in water with polarized light and crossed prisms, both before and after warming.

The gross appearance of the kidneys was not remarkable. However, the renal tubules of the dogs fed a diet low in protein uniformly showed a large excess of isotropic fat when compared with those of the control animals. There was little or no difference in the amount of fat found in the kidneys removed at operation and those removed later at autopsy.

It may also be pointed out that we found no significant changes in the blood cholesterol or fatty acids during the prolonged periods of observation.

PROTOCOLS

Dog 1.—This dog was an adult, smooth haired, female which weighed 18.4 Kg. She was fed a normal synthetic diet (Cargill) from Dec. 22, 1930, until Jan. 1, 1931, when she was placed on a synthetic diet low in protein (Cargill) with 0.3

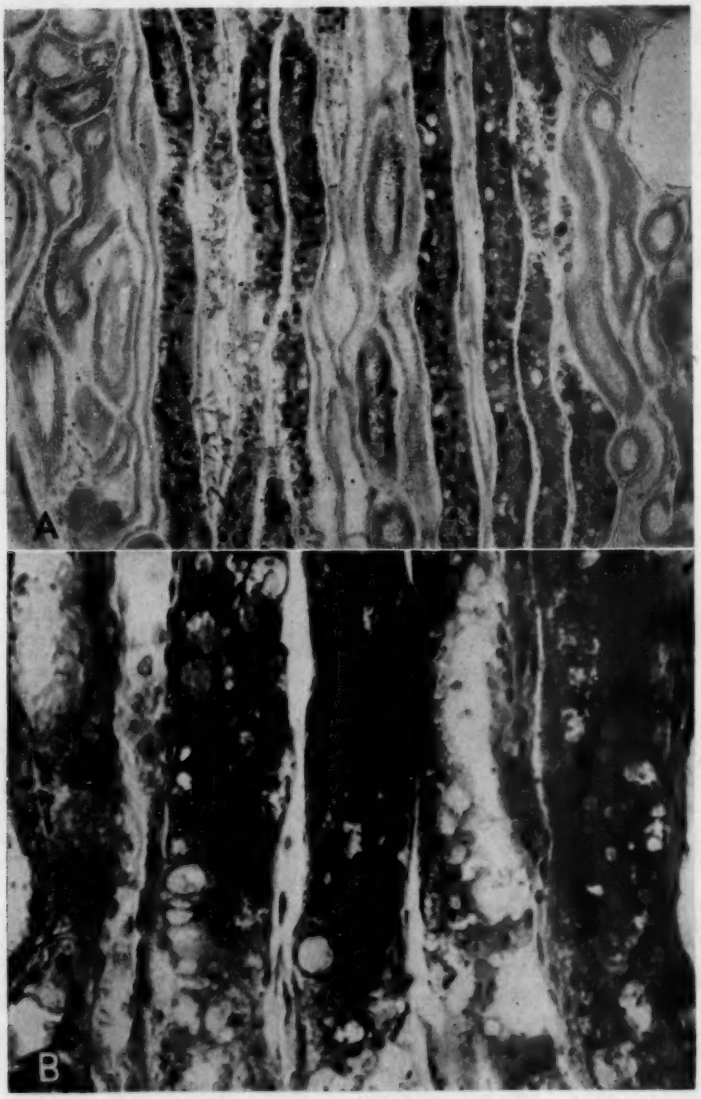
TABLE 3.—*Results in the Case of Dog 2*

Date	Weight, Kg.	Hematocrit, per Cent	Total Plasma Protein, Gm.	Plasma Albumin, Gm.	Plasma Globulin, Gm.	Fatty Acids, Gm.	Cholesterol, Gm.	Serum Phosphorus, Mg.	Blood Urea Nitrogen, Mg.	Diet	Comment
1/23/31	18.5	..	...	...	...	.....	.....	...	..	N	
1/23/31	18.5	53	6.7	5.2	1.5	0.165	0.190	3.5	14	LP	
2/24/31	15.3	..	...	...	...	.....	.....	...	..	A	
3/ 2/31	14.5	49	4.7	2.6	2.1	0.320	0.185	...	..	A	
3/27/31	13.3	38	4.5	2.4	2.1	0.290	0.250	...	..	A	
4/25/31	12.5	39	4.8	2.4	2.4	0.390	0.226	...	..	A	
5/20/31	11.5	34	3.7	2.0	1.7	.....	.....	...	..	A	
6/ 8/31	10.7	31	4.4	1.6	2.8	.....	0.284	...	4	A	1,000 cc. of 1 per cent solution of sodium chloride on 5 successive days
6/12/31	11.0	..	...	...	...	.....	.....	...	..	..	No edema
6/16/31	11.1	30	3.5	2.0	1.5	.....	.....	2.0	..	M	No edema; left nephrectomy
7/ 3/31	11.1	20	3.5	...	...	0.595	0.169	...	4	M	250 cc. of blood withdrawn
7/13/31	11.2	21	3.6	...	...	0.530	0.152	...	4	..	Autopsy

Gm. of protein per kilogram of body weight; this was continued until February 18. The dog was then fed diet A, described in the first paper of this series. We tried various forms of Cargill diets, but we found that after varying periods the dogs refused it, but they ate the vegetable diet (diet A) much better, though as a rule not all of it.

The total plasma protein had fallen to 4.6 Gm., with an albumin-globulin ratio of 3.0:1.5 by the eighty-sixth day. We then administered by gavage 1,000 cc. of a 1 per cent solution of sodium chloride on two successive days, but no edema was observed and there was no gain in weight. However, on the one hundred and fortieth day the total protein had dropped to 3.6 Gm., with an albumin-globulin ratio of 2.3:1.4; the administration of the same amount of salt solution produced extensive subcutaneous pitting edema and a gain in weight of 1.7 Kg. Nephrectomy was performed on the left side on the one hundred and forty-seventh day while the dog was still edematous. The dog was given a transfusion of 450 cc. of whole blood and was then fed a diet of milk and meat with a generous allowance of protein. However, after two days the plasma protein level had not changed

and the edema persisted. Edema disappeared on the fourth postoperative day, and on the sixth day the plasma protein had risen to 5.8 Gm., with an albumin-globulin ratio of 2.8 : 3.0.



Fatty changes in the renal tubules; sudan III stain. *A*, low power view; *B*, higher power view.

As we pointed out before, anemia gradually develops in animals fed this diet. We determined to control the effect of this factor on the fat deposit in the kidney by maintaining the anemia after the unilateral nephrectomy and allowed the plasma

protein levels to rise and then compared the pathologic picture of the remaining kidney with that of the one removed at operation. We were successful in maintaining the anemia by the withdrawal of large amounts of blood, but the expected rise in plasma protein levels did not occur. Doubtless the failure of the dog to eat all her food was a large factor in this disappointing result. Autopsy was performed on the forty-ninth postoperative day.

Autopsy showed, on external appearance, a marked emaciation. The muscles were pale, and the subcutaneous fat was almost absent. The left kidney was absent. The right kidney weighed 70 Gm. The capsule stripped with ease, leaving a smooth reddish-gray surface. The parenchyma of the kidney was of the usual consistency, and on section there was some yellow striation at the cortical medullary junction. Microscopic sections of the liver revealed a few large vacuoles within the cells throughout the lobule. The cytoplasm was coarsely granular and swollen. The sections of the kidney showed a large amount of fat, largely confined to the cells of the loops of Henle, and most of it stained red or lilac with nile blue sulphate. There was no doubly refractile lipoid in the especially prepared sections. There was no essential difference in the histologic picture in the right and the left kidney.

Dog 2.—This dog was an adult female gray police dog, weighing 18.5 Kg. She was fed a series of diets similar to those given to dog 1. On the fifty-fifth day, the total plasma protein was 4.5 Gm., with an albumin-globulin ratio of 2.4 : 2.1. At this time 1,000 cc. of salt solution was administered by gavage, but there was no gain in weight, and no edema appeared. This was repeated on the one hundred and ninth day, when the total protein was 3.7 Gm. and the albumin-globulin ratio 2.0 : 1.7, and again there was no gain in weight. On the one hundred and thirty-sixth day, the total plasma protein fell to 3.5 Gm., with an albumin-globulin ratio of 2.5 : 1.0, and again the administration of sodium chloride produced no edema.

Nephrectomy was done on the left on the one hundred and thirty-sixth day. The postoperative diet was the same as that given dog 2, and we again maintained anemia by the withdrawal of large amounts of blood. This dog also showed constantly low plasma protein levels after the operation. She was killed, and autopsy was performed on the twenty-ninth postoperative day. The autopsy report was essentially the same as that of dog 1.

Dog 3.—This was an adult, brown, female police dog, weighing 15.3 Kg. She was fed in the same way as dog 1. The total plasma proteins fell to 4.5 Gm., with an albumin-globulin ratio of 2.5 : 2.0 on the fifty-fifth day of the low protein feeding. At this time 1,000 cc. of a 1 per cent solution of sodium chloride was administered by gavage on two successive days, but no edema appeared. However, on the one hundred and ninth day the plasma protein had fallen to 3.7 Gm., with an albumin-globulin ratio of 2.2 : 1.5. At this time the same amount of salt solution was given, and extensive pitting edema developed with a total gain in weight of 1.7 Kg. This dog was so weak that the experiment had to be terminated on the one hundred and twenty-second day, when she was killed and autopsy was performed.

Autopsy showed nothing remarkable in the external appearance except moderate edema at the extremities, which also involved the subcutaneous tissues of the abdomen and thorax. The peritoneal cavity contained 75 cc. of clear light yellow fluid. There was edema of the walls of the stomach, and near the pylorus there were five small ulcers with indurated edges.

The kidneys were similar to those of dog 1, except that near the cortical medullary junction and extending from it into the cortex for a distance of 3 mm.

there was a radial deposition of yellow flecks in the tissue. The microscopic picture was similar to that in dog 1.

Dog 4.—This dog was an adult brown and black female weighing 18 Kg.; it was fed the same series of diets given to dog 2. On the eighty-third day the plasma protein had dropped to 4.9 Gm., and the albumin-globulin ratio was 2.9 : 2.0. During this time she was getting 1,000 cc. of a 1 per cent solution of sodium

TABLE 4.—*Results in the Case of Dog 3*

Date	Weight, Kg.	Hematocrit, per Cent	Total Plasma Protein, Gm.	Plasma Albumin, Gm.	Plasma Globulin, Gm.	Fatty Acids, Gm.	Cholesterol, Gm.	Serum Phosphorus, Mg.	Blood Urea Nitrogen, Mg.	Diet	Comment
1/23/31	15.3	..	...	...	...	.....	.....	...	..	N	
2/ 1/31	15.7	46	6.2	4.6	1.6	0.365	0.165	4.5	12	LP	
3/ 2/31	13.4	46	4.6	2.5	2.1	0.445	0.232	...	..	A	
3/27/31	11.7	39	4.5	2.5	2.0	0.350	0.199	...	..	A	
4/25/31	10.6	41	4.2	3.0	1.2	0.365	0.185	...	..	A	
5/20/31	9.3	28	3.7	2.2	1.5	.....	.....	...	..	A	
5/22/31	9.3	..	...	...	...	.....	.....	...	..	A	1,000 cc. of 1 per cent solution of sodium chloride on 2 successive days
5/26/31	11.1	20	3.2	1.4	1.8	.....	0.209	3.0	..	A	Edema
5/28/31	11.0	..	...	...	...	.....	.....	...	..	..	Edema
6/ 6/31	9.5	..	...	...	...	.....	.....	...	..	..	No edema; killed and autopsy performed

TABLE 5.—*Results in the Case of Dog 4*

Date	Weight, Kg.	Hematocrit, per Cent	Total Plasma Protein, Gm.	Plasma Albumin, Gm.	Plasma Globulin, Gm.	Fatty Acids, Gm.	Cholesterol, Gm.	Serum Phosphorus, Mg.	Blood Urea Nitrogen, Mg.	Diet	Comment
12/22/30	18.4	....	...	...	...	.....	.....	...	..	N	
1/ 3/31	18.0	45.6	7.0	4.5	2.5	0.275	0.145	4.2	17	LP	
2/24/31	12.5	....	...	...	...	.....	.....	...	..	A	
3/ 2/31	12.5	....	...	...	...	.....	.....	...	..	A	
3/27/31	11.3	40.0	4.9	2.9	2.0	0.340	0.200	...	..	A	
4/25/31	10.0	28.0	3.8	2.8	1.0	0.456	0.186	...	..	A	
5/20/31	8.3	33.0	4.2	2.4	1.8	.....	.....	...	..	A	1,000 cc. of 1 per cent solution of sodium chloride for 2 days
5/23/31	9.0	....	...	...	...	.....	.....	...	..	A	No edema
5/26/31	8.1	....	...	...	...	.....	.....	...	..	A	Died; no edema

chloride on two successive days, and there was no gain in weight. By the one hundred and thirty-seventh day, however, the plasma protein had fallen to 4.2 Gm., with an albumin-globulin ratio of 2.4 : 1.8. At this time the same amount of salt solution was administered, and she gained 0.7 Kg., but there was no demonstrable edema. This dog died on the one hundred and forty-third day.

Autopsy showed essentially the same changes as in dog 1.

Dogs 5 and 6.—These were control animals; they were fed a diet containing the same amount of fat per kilogram as diet A contained but an adequate amount of proteins (2.2 Gm. per kilogram). They consumed the diet well and were fairly healthy throughout with no evidence of anemia, and they gradually

gained weight. There was little or no change in the plasma protein levels. Autopsies were performed on the one hundredth day.

Autopsy revealed nothing of interest. The kidneys were normal in every respect. The sections stained with nile blue sulphate and sudan III showed very little fat. The difference in the amount of fat in these kidneys and in those of the experimental animals was striking.

SUMMARY AND CONCLUSION

Hypoproteinemia and edema were produced in two of four dogs fed a diet low in protein for a long time. A critical level of plasma proteins for the formation of edema in the dog is probably 4 Gm. of total protein per hundred cubic centimeters and 2 Gm. of plasma albumin.

The fatty changes in the renal tubules of all our dogs with hypoproteinemia were shown not to be accidental but the result of the experimental procedure. We are unable to prove that these fatty changes are not due to the anemia which invariably complicates these experiments, but we offer evidence that the anemia is not a potent factor. This fat is not the same as that found in the convoluted tubules in patients with the nephrotic syndrome, for in the dogs the fat is not in the form of doubly refractile spherocrystals.

LIPOID PNEUMONIA

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The rôle which the exogenous introduction of oily substances plays in the etiology of certain pathologic conditions of the lungs has aroused considerable interest in recent years because of the increasing use of a variety of oils in the treatment of diseases such as disturbances of the gastro-intestinal and respiratory tracts and vitamin deficiencies. The lesion produced in the lungs by the action of these oils consists essentially of a diffuse infiltration of the parenchyma with large monocytic cells, which engulf the oil in an attempt of the organism to dispose of it, together with other inflammatory cell infiltrates, such as plasma, eosinophilic and giant cells. After the inflammatory process subsides and healing takes place, there results local formation of fibrous tissue which replaces those portions of the parenchyma which previously had been the seat of the pneumonic process. Usually an acute inflammatory pneumonic superimposition occurs which causes death. This lesion has been termed lipoid pneumonia.

It has been established that similar pulmonary lesions can be produced in animals by the intratracheal injection of oily substances. Guieysse-Pellissier [1] showed that following such injection of olive oil in dogs or rabbits, the alveoli become filled with monocytes containing oil and many polymorphonuclear neutrophilic and esoinophilic leukocytes. Corper and Fried [2] described similar lesions in the lungs of animals following the use of olive oil, liquid petrolatum and chaulmoogra oil. Segal and Cohen, of this laboratory, confirmed these observations, in 1926, by intratracheal sprays of albolene in rabbits (unpublished experiments). In 1925, Laughlen [3] reported the case of an adult with paralysis of the larynx and vocal cords and the cases of three children

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From the Department of Pathology of the Jewish Hospital of Brooklyn.

1. Guieysse-Pellissier, A.: Compt. rend. Soc. de biol. **83**:809, 1920.
2. Corper, H. J., and Fried, H.: J. A. M. A. **79**:1739, 1922.
3. Laughlen, A. F.: Am. J. Path. **1**:407, 1925.

who showed large quantities of oil droplets with pulmonary changes similar to those described by Guieysse-Pellissier in experimental animals. He was also able to reproduce the lesion in the lungs of animals by the intratracheal injection of oily substances. In 1927, Pinkerton [4] reported six cases with findings similar to those reported previously. He observed, too, that the oily substance in the lungs is removed slowly, and that the end-picture of this process is fibrosis accompanied by giant cell formation. More recently, Pierson [5] reported a case of pneumonia in a child caused by aspiration of lipoids and gave a fairly detailed account of the findings in the lungs. He stated that the oil causes a profound and rapid reaction, which represents an effort on the part of the body to expel the foreign material. He expressed the opinion that pneumonia caused by lipoids is not common, although the realization of its possible existence may lead to more frequent diagnosis.

This paper has for its purpose a review of the subject to the present time and a presentation of six typical cases which illustrate this condition.

REPORT OF CASES

Case 1.—A girl, 9 weeks old, was admitted to the hospital on Nov. 29, 1925. Four days before the mother noted that the baby was fretful and in pain; this continued for three days. On the day before admission the patient took her feeding badly, was drowsy and irritable, became cyanotic and had several soft, greenish bowel movements. She was a normal infant, born at full term, had been cyanotic since birth, and had gained only 1 pound (4.5 Kg.).

The patient was very ill with a temperature of 97.2 F.; she was markedly cyanotic, and respiration was of a Cheyne-Stokes character. A brownish-red, mucoid material was expectorated frequently. There were dulness over the bases of both lungs and bronchial breathing. A loud systolic murmur was heard over the precordium. She died within three hours after admission. The red blood cells numbered 3,620,000; the hemoglobin was 75 per cent, and leukocytes numbered 27,000. A blood culture showed Staphylococcus anhaemolyticus. The clinical diagnosis was congenital heart disease and bronchopneumonia.

At autopsy the body was that of a poorly nourished infant. The heart was enlarged, and the mitral valve was covered with numerous vegetations. The ductus arteriosus was patent; the large vessels were transposed. The lungs showed a few pleural adhesions on the left side and a small amount of straw-colored fluid in the left pleural cavity. The upper lobe and the posterior portion of the lower lobe of the right lung and the entire posterior portion of the left lung were of a dark bluish color and firm. Microscopically, the discolored and firm portions showed an intense inflammatory process associated with atelectatic changes. The exudate was rather peculiar, as it consisted mainly of large monocytic cells

4. Pinkerton, H.: Am. J. Dis. Child. **33**:259, 1927.
5. Pierson, J. W.: J. A. M. A. **99**:1163, 1932.

which were heavily laden with fat globules. This cellular reaction was apparent everywhere, particularly within the lumens of the alveoli and, in places, within the alveolar walls. Some of the fat globules were extracellular, lying freely in the alveoli and alveolar walls. Associated with this lipoid process was a severe inflammatory reaction characterized by an exudate consisting of polymorphonuclear leukocytes and round cells (fig. 1).

Subsequent information from the mother revealed that the child's throat had been sprayed with an unidentified oily substance for some time.

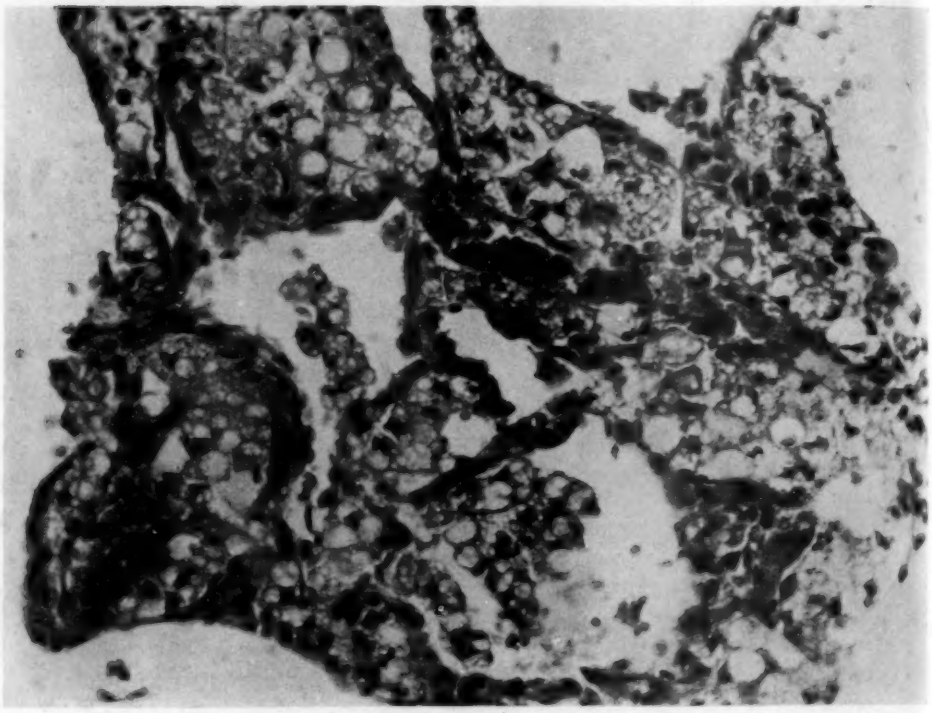

Fig. 1 (case 1).—Fat-laden monocytes within the alveolar spaces and alveolar walls of the lungs.

The following four cases present no history of aspiration of oily substances into the lungs, although postmortem examination showed their presence. In all of the cases, however, there was a history of vomiting, and it is possible that during vomiting small amounts of fat, perhaps from milk, were accidentally aspirated.

Case 2.—A boy, 6 months of age, was admitted to the hospital on Feb. 10, 1933, because of vomiting and diarrhea. He was apparently well until eight days before, when he had diarrhea with blood and mucus in the stools. His temperature was

104 F. two days before entrance and later fluctuated between 99 and 101 F. He was well developed and nourished. Respirations were slow and labored; the breath had an acetone odor. The lungs were normal on percussion and auscultation. The child died on the day following admission.

At autopsy, the lungs showed diffuse areas of consolidation. Microscopic examination of these areas revealed numerous large monocytic cells within the alveolar spaces. The cytoplasm of these cells was largely replaced by fat vacuoles which caused the cell to appear as a pale structure, while the nucleus was displaced toward the periphery. Other portions of the lung showed an acute pneumonic process with dense leukocytic infiltrations.

CASE 3.—A girl, 9 months old, was admitted to the hospital on Dec. 2, 1932, because of convulsions, underdevelopment and poor feeding. She showed evidence of an infection of the upper respiratory tract and of hypoglycemia. The liver was large, reaching to the brim of the pelvis. The temperature rose to 106 F., and the patient died on the day of admission.

At autopsy, the lungs showed diffuse areas of bronchopneumonia. Microscopically, many of the alveolar spaces in these areas were infiltrated with an abundance of large cells, the cytoplasm of which was replaced by multiple tiny fat vacuoles. In other areas the alveolar exudate consisted of large collections of polymorphonuclear leukocytes. Incidentally, the liver showed marked fatty changes, and the islands of Langerhans were markedly hypertrophied.

CASE 4.—A boy, 3 months of age, was admitted to the hospital on March 16, 1933, because of vomiting, fever and diarrhea. Two weeks before admission he had a temperature of 103 F., which later fluctuated between 102 and 106 F. He took his feedings poorly, vomited several times a day and later showed diarrhea. On admission he was acutely ill, drowsy and breathing rapidly. The tonsils and throat were deeply congested; he had bilateral otitis media. A few hours after admission he died.

At autopsy, there were found in the lungs patchy areas of consolidation, in which the alveoli and bronchioles showed microscopically a purulent exudate. Many of the alveolar spaces and bronchioles contained numerous large monocytic cells, the cytoplasm of which contained many small fat globules. Some of these cells were found within the alveolar walls and in the adjacent lymph spaces.

CASE 5.—A boy, 15 months of age, was admitted to the hospital on March 11, 1933, because of projectile vomiting, constipation and underweight. He was apparently well until the age of 5 months, when he began to have attacks of vomiting, which continued until admission. He was fairly well developed, irritable and apathetic. The lips were slightly cyanotic. The fingers and toes were clubbed. The heart and lungs were recorded as normal. Bronchopneumonia developed, and the patient died on April 3. The important observations at autopsy were confined to the kidneys and lungs, the former being the seat of an acute and subacute glomerulonephritis.

The lungs showed pleural adhesions at the apexes. In this region the pulmonary tissue was firm and consolidated. The rest of the lungs showed no significant changes. Sections from the apexes showed numerous large, pale cells within the alveoli. Many of these cells were filled with multiple tiny fat vacuoles.

The septums also contained many of these cells, as well as homogeneous globular bodies. Similar cells were found in the lymph spaces. Other patches showed the usual pneumonic changes.

The following case is of particular interest and therefore will be described in greater detail. It concerns a 4 year old child who suffered from encephalitis and bulbar paralysis and in whom a pneumonic process developed as the result of the long-continued administration of large amounts of cod liver oil.

CASE 6.—A boy, 4 years old, was admitted to the hospital on Nov. 14, 1931, because of inability to walk for the past five months. Following whooping cough at the age of 2 years, there developed symptoms indicative of encephalitis, with a high temperature, convulsions, loss of consciousness, cyanosis, frothing at the mouth and incontinence of urine and feces. He showed marked improvement during his stay in the hospital. He was readmitted, however, on Oct. 28, 1932, with symptoms of laryngeal paralysis and difficulty in talking and walking. On examination, there was evident a generalized spasticity of the extremities and of the back. All deep reflexes were exaggerated; the facial expression was fixed, and there was no display of emotion except when the child was crying. During his stay in the hospital, the temperature ranged between 99 and 100 F. until December 31, when encephalography was performed; 105 cc. of spinal fluid was removed, and 100 cc. of air was injected. On the following day he became stuporous and cyanotic; he had marked general convulsions and finally died.

At autopsy, the body was fairly well developed and well nourished. The lungs were voluminous and free from adhesions. The pleural surface was mottled with areas of pinkish-yellow discoloration which shaded into deep red toward the base. There were noted externally discrete purple-red nodules which were sharply demarcated from the surrounding lighter-colored surface and measured, on the average, from 5 to 6 mm. in diameter. These nodules felt firmer than the remainder of the lung and resembled small infarcts which had become impregnated with carbon. The cut surface of these nodules was distinctly firmer and drier than the surrounding parenchyma, while that of the remaining lung showed a diffuse purple-red discoloration and a moderately firm consistency. The bronchioles were considerably thickened and dilated and contained pus, mucus and frothy fluid. In the apical region of the right lung was a circumscribed abscess about 2 cm. in diameter, surrounded by a well formed pyogenic membrane and containing necrotic material mixed with thick yellow pus.

Microscopic examination of the lungs showed the essential lesion to be an inflammatory process in which large mononuclear cells formed the bulk of the exudate. These cells filled the alveoli and contained many fatty particles. The latter appeared as small spherical bodies, occupying the larger portion of the cell cytoplasm, with displacement of the nucleus toward the periphery. Large numbers of fat globules were also found in the alveoli and in the septums. Frozen sections showed these globules to be a fatty substance which stained bright red with scarlet red. The areas corresponding to the nodules described in the gross

showed local necrosis with an intense inflammatory reaction. The cells consisted chiefly of monocytes filled with fat droplets and to a lesser degree of polymorphonuclear leukocytes and plasma cells. The unaffected alveoli adjoining the pneumonic areas showed emphysema. The exudate in the abscess consisted mostly of leukocytes and to a smaller extent of fat-laden monocytes. Toward the periphery there were granulation tissue rich in capillaries and a fibroblastic process. Extracellular and intracellular oil droplets could be seen in fairly large numbers. Another striking feature in the lungs was peculiar nodular formations of concentric rings of epithelial, giant and fibroblastic cells, in many instances encysting

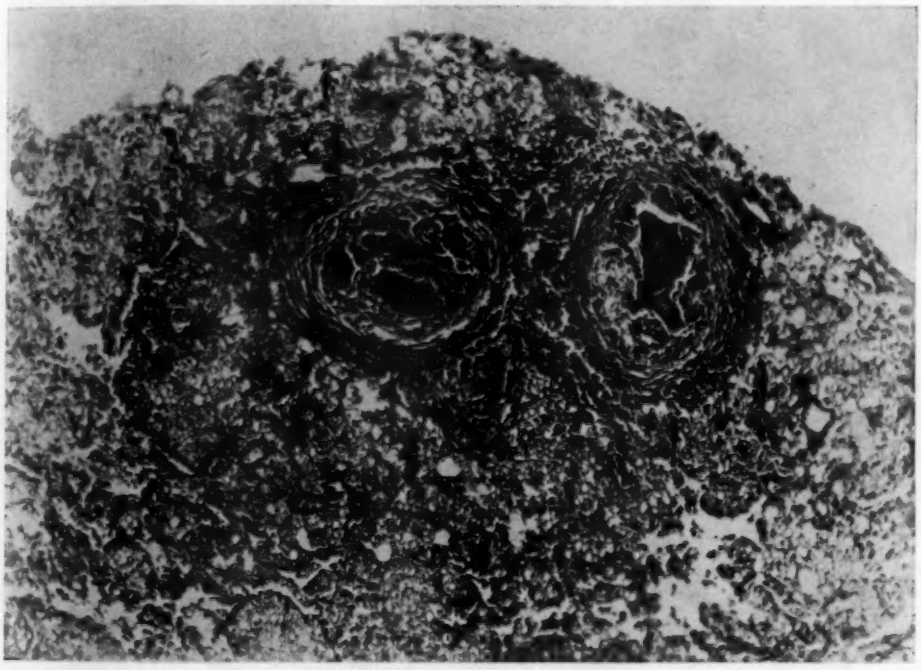

Fig. 2 (case 6).—Granulomatous areas in the lung, consisting of concentric rings of fibroblastic tissue, epithelial cells and scattered giant cells. In the midst of these are oil droplets.

in their midst fat vacuoles. The general appearance resembled tubercles. However, the epithelial cells which formed the most conspicuous part of the lesion simulated more the lining epithelium of the bronchioles. These lesions were interpreted as attempts to encyst the foreign material, similar in nature to granulomas caused by the presence of foreign bodies (figs. 2 and 3). The tracheobronchial lymph nodes contained fat-laden cells but were otherwise normal. In the brain, the left lateral ventricle was markedly dilated. Microscopically a widespread gliosis was noted, particularly in foci around the ventricular system. Microglia, especially the protoplasmic glia, were considerably increased.

The microscopic changes in the lungs of this patient were similar to those described by other authors. The formation of granuloma-like lesions typified a process peculiar to foreign body tissue reactions. The mode of entry of the foreign oily substance into the lungs is interesting. The mother stated that she had forced large quantities of cod liver oil

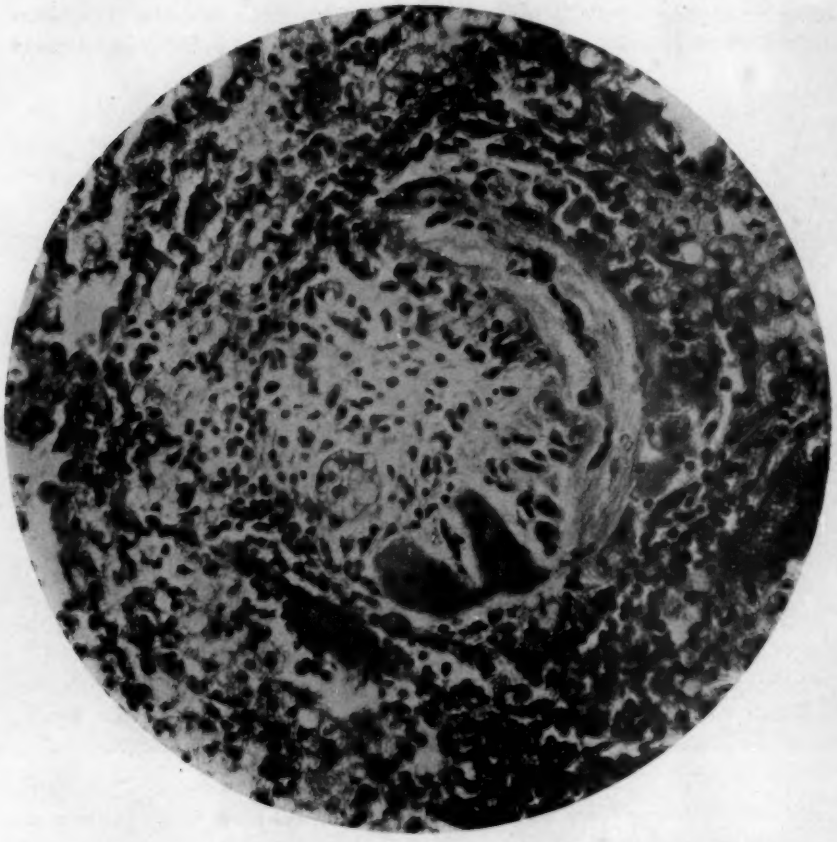

Fig. 3 (case 6).—High power photomicrograph of one of the granulomas, showing the presence of the oil-laden monocytes within this structure.

into the throat of the child for a long time in an attempt to improve his general health. It is probable that the child, already afflicted with encephalitis and bulbar paralysis, had lost the protective mechanism of preventing foreign matter from being aspirated into the lungs. As a result of this defect the oil apparently found its way into the lungs and was the cause of the lipoid pneumonia.

COMMENT

The appearances in these cases are striking and indicate certain significant conclusions. The pulmonary reaction to the oily material is much the same as that to any other foreign body. It consists of an inflammation which has for its main purpose, apparently, the ridding of the organism of the oily material. The cellular exudate in the alveoli and bronchioles consists for the most part of large monocytic cells which engulf the oil droplets and transport them to the local lymph channels and the regional lymph nodes. The chief interest centers, therefore, about the large monocytes, while the other cells which participate in the picture are of secondary importance. The latter cells are polymorphonuclear neutrophilic and eosinophilic leukocytes and plasma and giant cells. The fibrous tissue formation later in the disease is the end-result of the inflammatory lesion and represents an attempt at healing by scar tissue.

The formation of granulomas is of particular interest as a localized reaction to the oily substance, which results in the creation of concentric layers of epithelial cells, giant cells and fibroblastic tissue encysting droplets of oil. Thus, the foreign body substance is disposed of in at least three different ways: (1) expectorated with the monocytes, (2) taken up by the lymphatics or (3) encysted in the granuloma. These three ways of eliminating the oily substance may be seen in the same lung, although at times one process may predominate.

That the amount of oil and the length of time of administration have a definite bearing on the pulmonary lesions there can be no doubt. Moreover, that the chemical composition of the oil may have some influence on the pulmonary reaction has been suggested by some. If the quantity of oil which finds its way into the lungs is abundant and the administration is continued over a long time, the inflammatory reaction will be more intense and widespread. It has been shown, both clinically and experimentally in animals, that within a few minutes after the introduction of oil into the lungs there occur an inflammatory reaction and an invasion by large monocytes. The elimination of the oily substance, on the other hand, is slow. Since the introduction of iodized poppy seed oil as a diagnostic aid, cases of lipoid pneumonia due to this substance have been observed. One of us (J. R.) recently saw such a case following the intratracheal introduction of this substance in an old person who later died of bronchopneumonia. The lungs showed changes similar to those seen in lipoid pneumonia. The frequent use of oils in pediatric practice by way of the mouth and nasopharynx offers ample opportunity for the oil, especially in the very young, debilitated child, to find its way into the lungs.

Clinical and experimental evidence indicates that areas of lipoid pneumonia may occur without symptoms and signs in most cases.

The present study indicates the need for a change from the treatment of children by means of oily substances administered via the nasopharynx. It is evident that pulmonary inflammations due to the aspiration of lipoids are not detected often enough clinically. This is mainly because the initial lesion in the lungs is not sufficiently widespread to yield detectable clinical or roentgenologic signs. The diagnosis may be made, however, if a history of administration of an oily substance by way of the respiratory tract is obtained. It is also suggested that a careful examination of the expectorated material for monocytes containing oil droplets might be of value. Finally, serious pulmonary complications might be avoided by the more careful and controlled use and selection of oily substances for treatment by way of the nasopharynx, especially in young, debilitated children.

SUMMARY

Lipoid pneumonia occurs most frequently in infants. When it occurs in old persons it is usually due to laryngeal paralysis or to direct intratracheal introduction of oil.

The anatomic changes produced in the lungs by oil are characteristic and consist essentially of large monocytic cell infiltration and granulomatous formation. The greater portion of the oil is engulfed by monocytes and is either expectorated or carried to the regional lymphatics. Part of it is encysted in granulomatous tissue.

It is suggested that the diagnosis of lipoid pneumonia can be made in a certain number of cases by the examination of expectorated material for oily substances in the monocytic cells.

HISTOLOGY OF CERTAIN ORGANS AND TEETH IN CHRONIC TOXICOSIS DUE TO FLUORINE

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Studies on the growth and reproduction of rats receiving fluorides constantly as a part of the diet have recently been reported.[1] Large numbers of animals were used, and a systematic effort was made to determine the mechanism of the observed toxic effects by means of histologic examinations of all the principal organs. Some of the results of this survey are presented here.

The amounts of fluorine given to these animals were generally below the levels causing acute symptoms of toxicosis but were such as to produce evidence of chronic poisoning. The amounts used were between 15 and 30 mg. of fluorine per kilogram of body weight daily.

Reports in the literature on the effects of the ingestion of fluorine in comparable amounts exhibit variable results. Sollmann [2] stated that no histologic changes were produced by sodium fluoride when fed in amounts of from 50 to 150 mg. per kilogram of body weight per day. Kick [3] reported that the feeding of sodium fluoride had no effect on the liver, kidney, spleen, thyroid or parathyroid of rats. He found that 1 per cent of rock phosphate did not cause degeneration of the epithelium of the convoluted tubules in the kidney of the rat. Hauck, Steenbock and Parsons [4] could detect no histologic changes in eighty-eight parathyroid glands, sectioned serially, from rats fed 0.15 per cent sodium chloride. They mentioned degenerative changes in the kidney

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From the Department of Agricultural Chemistry, University of Wisconsin.

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1. (*a*) Lamb, A. R.; Phillips, P. H.; Hart, E. B., and Bohstedt, G.: Am. J. Physiol. **106**:305, 1933. (*b*) Phillips, P. H.; Lamb, A. R.; Hart, E. B., and Bohstedt, G.: ibid. **106**:356, 1933.

2. Sollmann, T.: A Manual of Pharmacology, ed. 3, Philadelphia, W. B. Saunders Company, 1926.

3. Kick, C. H.: Thesis, University of Wisconsin, 1930.

4. Hauck, H. M.; Steenbock, H., and Parsons, H. T.: Am. J. Physiol. **103**: 480, 1933.

and testes. Cristiani [5] studied the histologic changes in the hypophysis cerebri and the thyroid glands of guinea-pigs suffering from fluorosis. Macroscopically, the hypophysis was reported to be diminished in size and volume. Microscopically, the reduction in size of the gland was due to atrophy of the cellular elements. The connective tissue stroma was distended and the blood vessels showed dilation which gave the appearance of chronic passive congestion to the gland. The acinal cells were reported to have become smaller in size and poor in cytoplasm which was remarkably free of granular material. Small amounts of sodium fluoride caused a proliferation of the parenchymatous tissue of the thyroid gland in 14 experimental animals. Chaneles [6] studied the histologic changes in rats fed a diet of milk and bread plus 50 mg. of sodium fluoride per kilogram of body weight per day. His examination of the thyroid gland, testes, suprarenal glands, heart, spleen, liver, kidney and bone yielded negative results except for slight congestion in the liver, spleen and suprarenal glands.

Goldenberg [7] reported that a daily intake of from 2 to 3 mg. of sodium fluoride caused hypertrophy of the thyroid gland in the rat, and that sodium fluoride administered either orally or intravenously ameliorated the clinical symptoms of exophthalmic goiter. Tolle and Maynard,[8] however, found no differences in the weight of the thyroid gland between controls and fluorine-fed rats.

EXPERIMENTAL METHOD

Tissues were taken for histologic examination from the animals used in the studies previously described.[1] In all, 1,798 preparations representing more than 300 animals were made. The tissues thus obtained represent experimental animals fed various amounts of sodium fluoride or rock phosphate and their controls. The basal diet, which is given in detail in the papers cited, contained yellow corn, wheat middlings, linseed oil meal, alfalfa meal, tankage, ground limestone, bone meal and sodium chloride. The rock phosphate contained 3.52 per cent fluorine. The additions to the basal diet were given under a variety of experimental procedures, but in most cases they were given throughout the life of the animal. In groups A-1, A-3 and A-7 second, third, fourth and fifth generation rats are included.

The tissues taken for study were: liver, kidney, thyroid, suprarenal, hypophysis, ovary, testes, femur and incisor teeth. These tissues were fixed in the

5. Cristiani, H.: Compt. rend. Soc. de biol. **103**:556, 745 and 981, 1930; **107**: 554, 1931.

6. Chaneles, J.: Rev. Soc. argent. de biol. **5**:386, 1929.

7. Goldenberg, L.: Compt. rend. Soc. de biol. **95**:1169, 1926; Semana méd. **2**:1659, 1932.

8. Tolle, C., and Maynard, L. A.: Cornell University Agricultural Experiment Station, Bull. 530, 1931.

usual manner in a trinitrophenol-formaldehyde solution[9] or in Zenker's fluid to which a dilute solution of formaldehyde was added; they were dehydrated in graded alcohol and embedded in paraffin. In the case of the bones and the teeth, decalcification was effected by means of 5 per cent nitric acid in 70 per cent alcohol during the dehydration process. A few teeth were fixed, dehydrated, embedded in balsam and ground thin for examination of the enamel layer. All sections were stained with hematoxylin and eosin in the usual manner.

RESULTS

The microscopic appearance of the tissues was quite normal in comparison with the severe gross symptoms of chronic fluorosis. At the moderate levels used in the greater part of these experiments the glands and organs concerned with reproduction were unaffected. The high level of 0.30 per cent sodium fluoride caused marked degenerative changes in the testes. The ovaries, hypophysis and suprarenal glands were in most cases normal, although fatty degeneration was noted in the suprarenal glands in a few cases and there was a tendency toward passive congestion of this gland as indicated by the distended appearance of the blood vessels and sinusoids, particularly in the region of the zona reticularis of the medulla.

The deviations from the normal histologic appearance most frequently observed in the soft tissues were in the kidney and thyroid gland. Frequently ecchymotic or petechial hemorrhages occurred which might be taken as evidence of toxemia. These hemorrhages occurred in the endocardium and particularly in the mucosa of the pylorus. Hemorrhages of the pylorus in fluorine-fed rats were also observed by Hauck and her co-workers.[4]

The deviation most often noted in the thyroid gland was a change in the epithelial elements (fig. 1). The normal uniformly low cuboidal cells lining the acinus changed into a low columnar type of cell resembling a parenchymatous proliferation. The changes noted were not extensive, and in most cases a portion of the gland retained its normal appearance. The character of the colloidal material was less frequently changed. There seemed to be a tendency toward more desquamation of the epithelial cells in the animals receiving fluorine. High levels of fluorine intake over short periods of time failed to produce these changes. There was some evidence of occasional fibrosis.

The kidney was most frequently affected. The nature of the changes were usually those of parenchymatous degeneration in the convoluted portion of the renal tubules, and occasionally hyaline degeneration in the blood vessels (fig. 2). In acute cases the tubules became greatly distended. Macroscopically, the kidney became spotted.

9. Solution of formaldehyde, U. S. P., 500 cc.; distilled water, 1,875 cc.; glacial acetic acid, 125 cc.; trinitrophenol to saturation point.

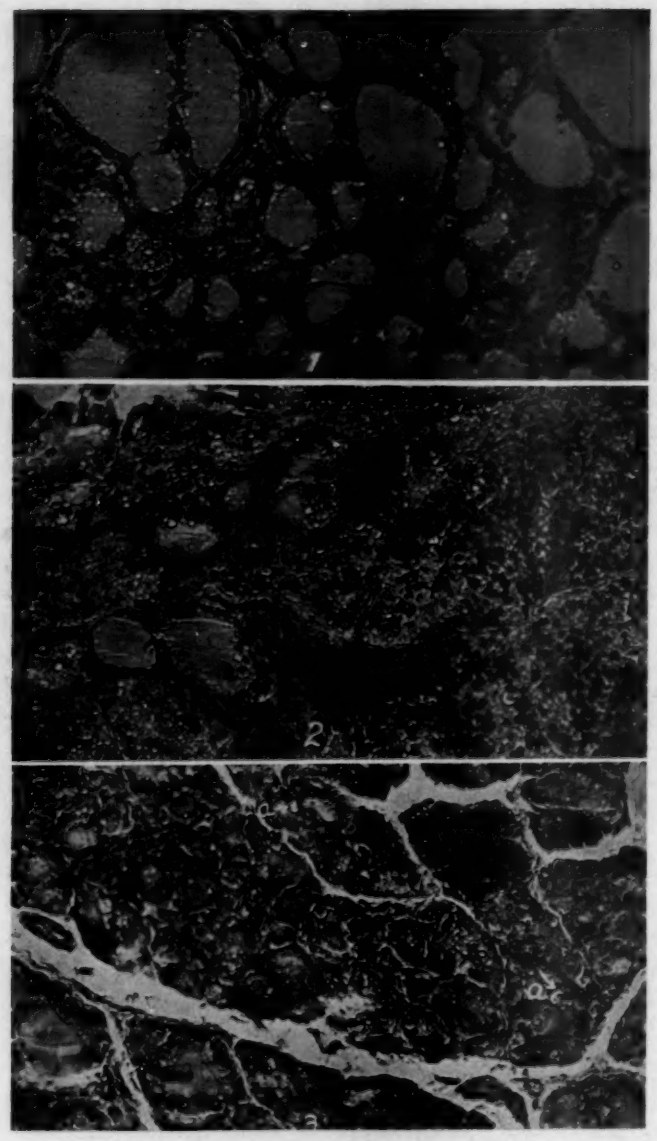

Fig. 1.—The thyroid gland: *1*, thyroid gland from a normal rat fed the basal A-1 ration; × 500. *2*, thyroid gland from a rat fed the basal A-1 ration plus 1 per cent rock phosphate which contained 3.5 per cent fluorine. Cellular infiltration and fibrosis are evident in this portion of the gland; × 500. *3*, thyroid gland from a rat fed the basal A-1 ration plus 0.043 per cent sodium fluoride. The acinal cell is distinctly transformed into a parenchymatous proliferative type of cell. The presence of numerous large cells with transparent cytoplasm is apparent (*a*). These acini in this gland suggest changes caused by fasting; × 500.

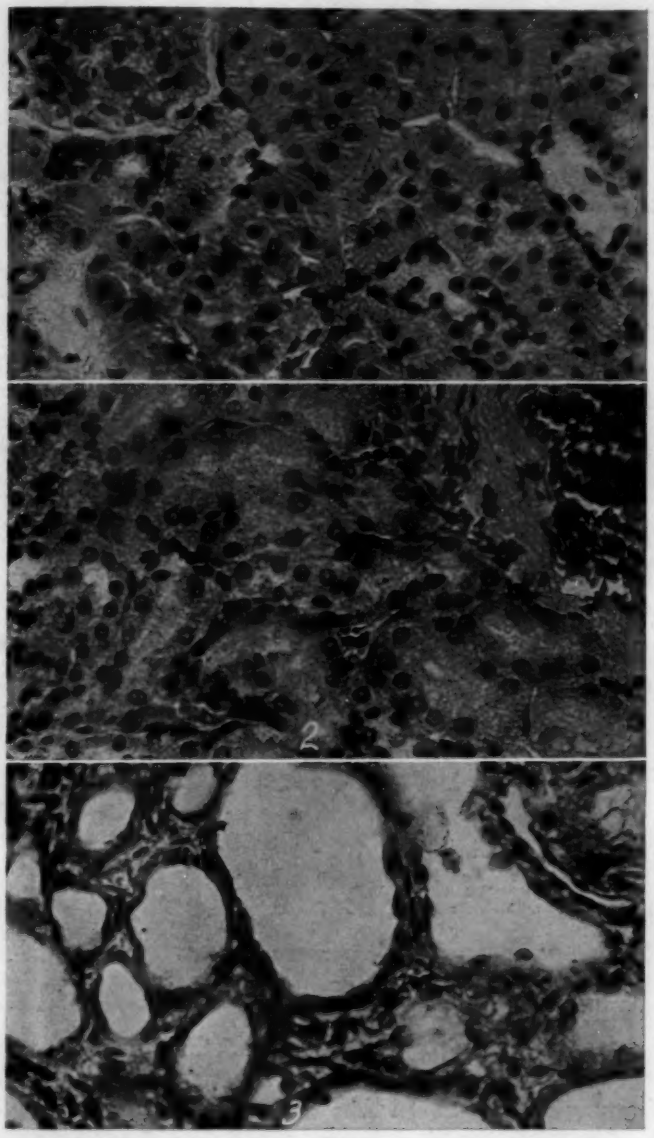

Fig. 2.—The kidney: *1*, kidney from a rat fed the basal A-1 ration; × 500. *2*, kidney from a rat fed the basal A-1 ration plus 1 per cent rock phosphate which contained 3.5 per cent fluorine. The disappearance of occasional nuclei and the occurrence of pyknosis indicate degenerative changes in this portion of the kidney. A hemorrhagic area is present; × 500. *3*, kidney from a rat fed the basal A-1 ration plus 0.15 per cent sodium fluoride. This represents the severe effects of fluorine on the kidney. It is marked by considerable dilatation and distention of the renal tubules. In most cases much cellular débris is found in the lumen of the tubules, and occasionally renal casts are seen; × 500.

The table indicates that the testes, ovaries and liver were also affected to some degree. Except at the higher levels of fluorine intake, the degeneration of the testes may have been influenced by senility, as the only male showing testicular degeneration at a low fluorine intake was approximately 15 months old, and this change is not infrequently noted in control animals at this age. In the A-3 and A-7 lots the females showing changes in the ovaries had all produced one litter each and subsequently failed to become pregnant. In these cases persistent corpora lutea were present and few or no developing follicles were observed. The changes observed in the liver were those of fatty degen-

Summary of the Frequency of the Occurrence of Histologic Changes in Soft Tissues Noted in Animals on Fluorine Diets as Compared with Controls

	A-1 or Basal Ration			A-3 or Basal Plus 0.043% Sodium Fluoride			A-6 or Basal Plus 0.6% Rock Phosphate			A-7 or Basal Plus 1% Rock Phosphate		
Tissue	No. of Animals	Abnormal	Per Cent Abnormal	No. of Animals	Abnormal	Per Cent Abnormal	No. of Animals	Abnormal	Per Cent Abnormal	No. of Animals	Abnormal	Per Cent Abnormal
Liver	33	0	0	44	1	2.9	8	0	0	44	1	2.3
Kidney	44	6	13.7	49	22	44.9	7	2	28.6	46	14	30.4
Thyroid	38	4	10.8	43	19	44.1	5	3	60.0	46	10	21.9
Suprarenal	39	0	....	43	5	11.6	2	..	0	45	2	4.4
Ovary	24	0	....	18	3	16.6	3	..	0	29	3	10.5
Testis	9	0	....	9	1	11.1	2	..	0	10	0	....
Hypophysis	2	0	....	6	1	16.6	..	..	....	..	..	....

	Basal Plus 0.10% Sodium Fluoride			Basal Plus 0.20% Sodium Fluoride			Basal Plus 0.30% Sodium Fluoride		
	No. of Animals	Abnormal	Per Cent Abnormal	No. of Animals	Abnormal	Per Cent Abnormal	No. of Animals	Abnormal	Per Cent Abnormal
Liver	3	0	0	4	1	25.0	6	1	16.6
Kidney	3	1	33.3	4	1	25.0	6	3	50.0
Ovary	2	0	0	1	0	0	2	0	0
Testis	2	0	0	3	0	0	3	3	100.0

eration, which occurred in 2 cases, and occasionally intracellular edema was noticed. These changes may or may not have been due to the effects of the fluorine.

A total of 122 decalcified slides prepared from the maxillae and mandibles with cross-sections of the teeth, and also of the radius and ulna of young rats up to 8 weeks of age, showed no variation from normal. The teeth exhibited normal pulp, characteristically arranged odontoblasts, well developed dentinal tubules, and apparently normal calcification of the dentin. Abnormal calcification of the long bones was not detected at this age.

The bleaching effect of fluorine on the teeth of rats has been described in general terms by other workers. It is interesting to observe the development of this phenomenon in mature animals fed our basal ration plus 0.15 per cent sodium fluoride. The bleaching effect is first noticed on the mandibular incisors between the fourteenth and sixteenth

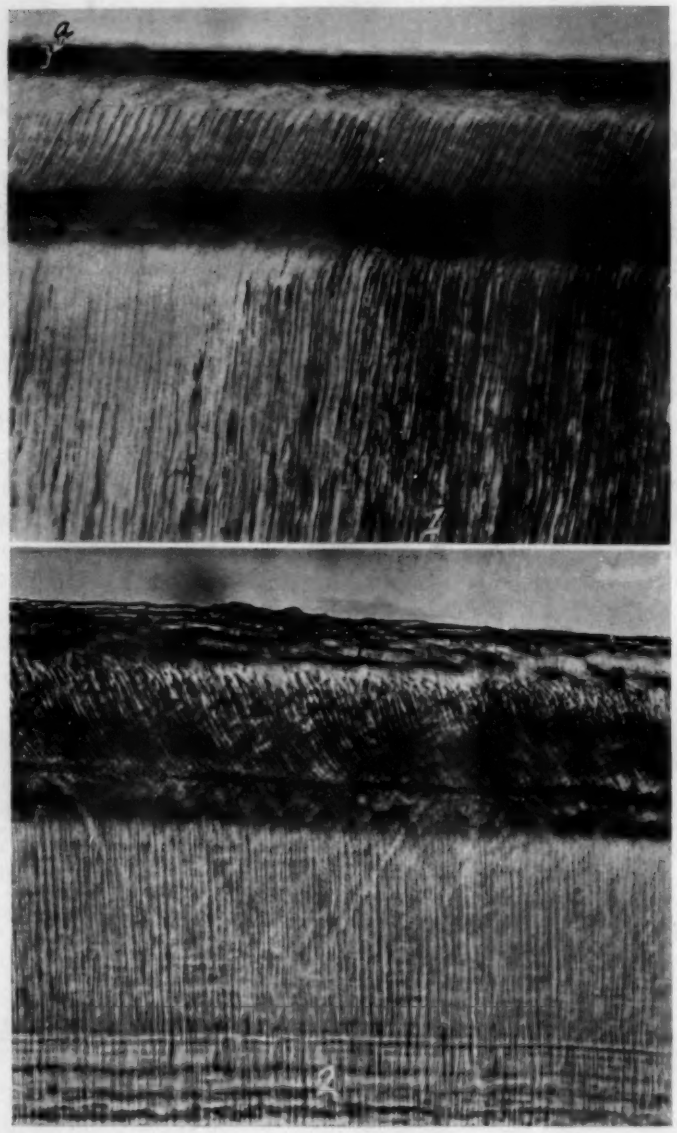

Fig. 3.—The teeth: *1*, a ground section of a tooth from a rat fed the basal A-1 ration. Note the regular and uniform enamel rods and the outer dark band (*a*) which represents the amber-colored surface of the normal enamel in the rat tooth; × 200. *2*, a ground section of a tooth from a rat fed the basal A-1 ration plus 0.15 per cent rock phosphate until the amber color was lost, approximately thirty days. This tooth was ground somewhat thinner than the section in *1*. Note the "flaky" character and loss of density of the outer portion of the enamel layer; × 200.

day after the incorporation of the sodium fluoride in the ration. It is first noticeable as a white chalky band at the base of the teeth. The band widens rapidly, ascending the tooth and causing a change from the normal amber color of the anterior surface of the tooth to a chalky lusterless white. There is a distinct line of demarcation between the two sections of the tooth, and the progress of the decoloration is easily followed. Usually the bleaching of the full length of the tooth requires from ten to twelve days. The mandibular incisors bleach first, followed by the maxillary incisors in the same manner. Both pairs of incisors are thus completely bleached in approximately fifty days. Coincident with the bleaching there is a failure to wear normally, and the usual chisel edge is lost. The teeth become thickened and elongated, with the increase in size due principally to an increase in the dentine.

Ground sections of these teeth present a defective enamel in the outer one third of this structure (fig. 3). While there seems to be a tendency to a more widely dispersed area of Tomes, the chief variation from normal lies in the colored portion of the enamel. The enamel rods appear to be normal in size, length and form, but the outer portion becomes flaky and loses the compact appearance and the color present in the normal tooth. Abnormal calcification appears likely and suggests either defective calcification or removal of calcium. Chipping of this outer layer is noticeable in teeth from rats which have been subjected to a long-continued ingestion of fluorine.

SUMMARY AND CONCLUSIONS

Histologic changes have been observed as the direct result of including fluorine in the diet of rats, either in the form of the sodium salt or as rock phosphate. Degenerative changes were found most frequently in the kidneys, with degeneration of the testes at the higher levels of ingestion of fluorine. The degree of deviation from the normal histologic appearance was closely related to the level of the fluorine ingested. The histologic appearance of the hypophysis remained practically normal, which is in harmony with the fact that it maintains its normal weight and functioning power [1b] with respect to gonadal stimulation. No reduction in size of the gland and no atrophy of the cellular elements were observed. A mild parenchymatous proliferation occurred in the thyroid gland when sodium fluoride was fed. No gross hypertrophy of this gland was observed.

These studies of toxicosis due to the ingestion of fluorine indicate that fluorine produces pathologic changes in the kidneys, incisor teeth and thyroid glands in the rat when from 20 to 30 mg. of fluorine per kilogram of body weight is ingested daily. To a lesser and more variable extent, pathologic changes have been noted in the liver and suprarenal glands. Pathologic changes in other tissues were not detected.

NATURE AND ORIGIN OF THE XANTHOMA CELL

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During the past half century much work has been done and many observations recorded dealing with xanthomatous processes. In this study an attempt has been made to determine the origin and more particularly the nature of the fundamental cell common to these processes—the xanthoma cell or foam cell.

The material studied in the preparation of this paper included eleven cases from the surgical laboratory of the Toronto General Hospital, six cases from the laboratories of the Department of Health, Ontario, and two cases from the Hospital for Sick Children, one of which was an example of Gaucher's disease. In all but the latter case, the xanthoma nodules were removed by surgical procedures since 1929, making a total of eighteen specimens.

Xanthoma has been found in nearly every tissue of the body.[1] Probably the most frequently seen type of xanthoma is the so-called xanthelasma palpebrarum. The disease appears as flattened yellowish plaques on the upper eyelids of older people. The next most common type is the xanthoma of the tendon sheaths. Certain conditions, such as diseases of the liver with icterus, nephritis and diabetes, are frequently associated with the formation of xanthoma. Specialized types of xanthoma forming definite clinical syndromes, such as Schüller-Christian's disease, Gaucher's disease and Niemann-Pick disease, are not common. The familial incidence of xanthoma has been observed and recorded by many.[2]

Xanthoma usually presents a typical appearance in the gross. It is remarkable that as a general rule one may recognize xanthoma and similar processes by their peculiar color. The typical xanthelasma seen on the upper eyelids of persons past middle life presents a yellowish-orange color, sometimes with a grayish tint. This color may or may not be seen in other types of xanthoma, as in xanthoma diabeticorum,

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From the Department of Pathology and Bacteriology, University of Toronto.

1. Finney, W. P.; Montgomery, H., and New, G. B.: J. A. M. A. **99**:1071, 1932.

2. Schmidt, E.: Arch. f. Dermat. u. Syph. **140**:408, 1922. Arning, E., and Lippmann, A.: Ztschr. f. klin. Med. **89**:107, 1920. Llambias, J., and Celesia, A.: Rev. Soc. argent. de biol. **1**:291, 1925; abstr., J. A. M. A. **85**:1764, 1925. Hufschmitt, G., and Nessmann, V.: Ann. de dermat. et syph. **1**:462, 1930. Wile, U. J., and Duemling, W. W.: Arch. Dermat. & Syph. **21**:642, 1930.

which usually has a zone of redness about the borders of the nodule. Or again, in xanthoma tuberosum and xanthoma multiplex, the color may not be obvious from the surface. If, however, one incises such a nodule, the typical egg-yolk color may be seen. In this regard it is noteworthy that atheroma of the arteries is identical in color to xanthoma. The color here may be modified considerably by the occurrence of atheroma in a large plaque of chronic nodular endarteritis, in which case the yellowish color may be faintly seen through the layer of the pearly white endarteritis. Furthermore, in locations where the tissues have been involved in chronic suppurative reaction, masses presenting this typical color may be seen; for example, chronic empyema, chronic abscess of the brain and chronic suppurative salpingitis. Smith [3] claimed that this color may be due to a colored lipoid, an endogenous melanotic pigment, blood pigment or a combination of these. Garret [4] ascribed the color to blood pigment. Miller [5] claimed that carotene and xanthophyll, belonging to the group of carotinoids, when combined with cholesterol esters, which themselves are colorless, give rise to this color.

In preparing microscopic sections for study, the following stains were used after embedding in paraffin: hematoxylin and eosin, Mallory's connective tissue stain, phosphotungstic acid-hematoxylin and Masson's stain. A special study was made of frozen sections which were stained with sudan III and nile blue, and further differentiation was obtained by the use of the polarizing microscope.

Pollitzer and Wile [6] grouped their microscopic observations into three stages: the smallest and youngest lesions, the stage of proliferation and the stage of retrogression. Their findings were in general substantiated by the present series. In the earliest lesions a few foam cells may be seen in intimate relationship to the adventitia of small blood vessels. These cells vary from 10 to 25 microns in diameter. They are very pale in paraffin sections. A fine thin cell membrane encloses a cytoplasm which consists of very delicate strands forming tiny, round, oval and slitlike spaces. The cytoplasm is slightly basophilic in reaction. The nucleus is usually centrally placed and is large and generally pale-staining; frequently a nucleolus can be seen. In sections stained with sudan III, tiny red globules can be seen to fill most of the cell. Sometimes these globules are larger and fewer. When nile blue is used, these globules stain faintly pink, deep blue or an intermediate mauve to purple. Under the polarizing microscope a small amount of doubly refractile substance can be seen. These fat-staining reactions indicate a mixture of lipoid substances, and since the nucleus shows no

3. Smith, D. T.: Arch. Surg. **8**:908, 1924.
4. Garrett, C. A.: Arch. Surg. **8**:890, 1924.
5. Miller, quoted by Rowland, R. S.: Ann. Int. Med. **2**:1277, 1929.
6. Pollitzer, S., and Wile, U. J.: J. Cutan. Dis. **30**:235, 1912.

qualities demonstrative of a degenerative process, it is assumed that this lipoid material has been phagocytosed by the aforementioned cells.

In later lesions, the number of foam cells is greatly increased. Individually, they are larger, measuring up to 40 microns in diameter. The lipoid globules become smaller. There is a more definite appearance to the cytoplasm. It appears as a fine network of a reticulated character, slightly basophilic in reaction. The nucleus is sometimes swollen, and the chromatin network is coarse and deeply stained. Other nuclei are pale and dotted with finely granular chromatin, and usually an eccentric nucleolus is present. There is considerable fibrous connective tissue round about masses of the foam cells. Some of the individual foam cells appear compressed and elongated by pressure from the surrounding fibrous tissue cells. Occasionally, with fat stains, fibroblasts may be seen to contain a small amount of lipoid material, none of which, however, is doubly refractile to polarized light. In a large clump of foam cells, the more central cells may become polygonal. Occasionally a large cell may be seen with two or three nuclei and foamy cytoplasm, evidently a stage in the formation of a Touton giant cell. This picture is to be differentiated from the foreign body giant cell, which infrequently may be seen enclosing a long narrow slit, representing the position of a cholesterol crystal which has been dissolved in the preparation.

At a later stage there is a still greater increase in the connective tissue element, which at times closely resembles granulation tissue. The foam cells are of a more uniform size. Many cells having the appearance of giant cells may, on closer examination, be seen to be true giant cells, or, on the other hand, a thinning of the cell membrane may closely simulate this condition. On examining this stage with Nicol prisms, the cholesterol content of the cells appears to have definitely increased, although the reactions to the fat stains remain as before.

In none of the cases examined was the xanthoma seen to extend into the epidermis or below the deep fascial layers. In every case the lesion was limited to the subcutaneous tissues, which in these areas were more or less thickened.

In my observations on the fatty character of these lesions, nile blue was used to distinguish neutral fat from fatty acid, the former staining red and the latter blue. Thus the lipoid constituent of xanthoma was found to be composed of cholesterol and its esters, neutral fats and fatty acids. Probably the most important and constant of these is cholesterol and its esters. The relation between these lesions and a possible disturbance of cholesterol metabolism has thus been the object of great attention.

Many authors have observed and reported cases of xanthoma associated with hypercholesteremia (Ingram,[7] Hoessli[8] and others). A few have reported the blood cholesterol as normal or even subnormal.[9] In this regard Bloch[10] pointed out that low serum cholesterol was the exception rather than the rule. He showed that the lipoid system of the blood consisted of the insoluble substances cholesterol, phosphatides, neutral fats and fatty acids, which were present in a finely dispersed stable emulsion, and soaps, which were soluble. Proportions of the substances, if changed sufficiently from the normal, resulted in a disturbance of the stable emulsion, the particles becoming larger and coarser and, granted favorable conditions, being precipitated to form xanthoma. Thus, Bloch showed that determination of only one constituent (viz., cholesterol) was not conclusive in establishing the presence or absence of a disturbance of lipoid proportions.

Disturbance of lipoid metabolism and especially hypercholesteremia can thus be seen to play an important etiologic rôle in the production of xanthoma.

Such conditions as jaundice[11] and diabetes (Finney, Montgomery and New,[1] Major[12] and others) are frequently precursors to the formation of xanthoma. Numerous other authors (Engman and Weiss,[13] Mook and Weiss[14] and others) have observed the disappearance of xanthoma in these cases with suitable diet or treatment with insulin.

Trauma as an etiologic factor has been advanced by several writers. The frequent occurrence of xanthoma of the tendon sheaths possibly bears some relation to friction as a localizing factor. Chauffard[15] presented a case in which xanthoma developed at the site of hypodermic injections of sodium cacodylate, the patient having a preexisting hypercholesteremia. Ochs[16] described a case in which xanthoma developed at the sites of injection during treatment for syphilis and in which a series of lesions developed around the vaccination scar. Many experimenters have produced a state of hypercholesteremia in animals, espe-

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7. Ingram, J. T.: Brit. J. Dermat. **39**:335, 1927.

8. Hoessli, H.: Beitr. z. klin. Chir. **95**:185 and 198, 1914.

9. Rosenthal, F., and Braunisch, R.: Ztschr. f. klin. Med. **92**:429, 1921. Rosenbloom, J.: Arch. Int. Med. **12**:395, 1913.

10. Bloch, B.: Brit. J. Dermat. **43**:61, 1931.

11. Hutchinson, J.; Sangster, A., and Crocker, H. R.: Tr. Path. Soc. London **33**:376, 1882.

12. Major, R. H.: Bull. Johns Hopkins Hosp. **35**:27, 1924.

13. Engman, M. F., and Weiss, R. S.: Arch. Dermat. & Syph. **8**:625, 1923.

14. Mook, W. H., and Weiss, R. S.: Arch. Dermat. & Syph. **8**:19, 1923.

15. Chauffard, quoted by McWhorter, J. E., and Weeks, C.: Surg., Gynec. & Obst. **40**:199, 1925.

16. Ochs, B.: Arch. Dermat. & Syph. **22**:922, 1930.

cially the rabbit, by feeding them a diet high in cholesterol. Anitschow [17] produced subcutaneous sterile abscesses in rabbits in this state and produced typical xanthoma. Weidman [18] produced a similar condition in dogs. Chuma [19] produced xanthosis and xanthoma in rabbits under similar circumstances. Anitschow also produced localized xanthoma in hypercholesteremic rabbits by repeated trauma to the skin over the tendo achillis and by freezing the skin with carbon dioxide.

From the foregoing remarks it would appear that disturbance of cholesterol metabolism is of definite etiologic significance, and that trauma may be a factor in the localization of the xanthomatous process.

In a similar manner, the so-called atheroma may be experimentally produced by feeding animals a diet high in cholesterol.[20] The first lesions produced by experimental methods are the fine superficial fatty streaks.[20d] If carried for a sufficient time, atheroma may be produced.[21] Klotz found that the name "atheroma" was given by Haller in 1755 to "callosities and yellow spots projecting into the arterial lumen from which a soft pultaceous material could be expressed."

In the gross the appearance of atheroma simulates that of xanthoma remarkably. The peculiar yellowish-orange color is an outstanding feature. Atheroma appears as localized, flattened nodules or plaques slightly raised above the remainder of the intimal surface. It has, however, two features which are not seen in xanthoma: (1) On incising the intimal covering, a grumous, slimy, yellowish material may be squeezed out; and (2) there is a tendency toward calcification with advancing years.

On microscopic examination a significant finding, which sometimes is very marked, is the presence of foam cells. These have an appearance identical to that of the foam cells discussed previously as xanthoma cells. The features of the large pale cell with very fine vacuoles, giving to the cytoplasm a finely reticular structure in sections prepared with alcohol, may be seen. The size of these cells varies from 10 to 35 microns. The nuclei usually stain well but show no evidences of degeneration. Moreover, on employing fat stains, the material in these cells may be seen to consist of cholesterol esters, fatty acids and neutral fats.

Even in the earliest lesions of fatty nature in the intima, that is, superficial fatty streaks, foam cells may be seen.[20d] These cells are large

17. Anitschow, N.: (*a*) München. med. Wchnschr. **60**:2555, 1913; (*b*) Beitr. z. path. Anat. u. z. allg. Path. **57**:201, 1914.

18. Weidman, F. D.: Arch. Dermat. & Syph. **15**:659, 1927.

19. Chuma, M.: Virchows Arch. f. path. Anat. **242**:275, 1923.

20. (*a*) Klotz, Oskar: Brit. M. J. **11**:1767, 1906; (*b*) J. M. Research **33**:157, 1915; (*c*) Centralbl. f. allg. Path. u. path. Anat. **19**:535, 1908; (*d*) Duff, G. L.: Experimental Cholesterol Arteriosclerosis, to be published.

21. Klotz, Oskar: J. M. Research **32**:27, 1915.

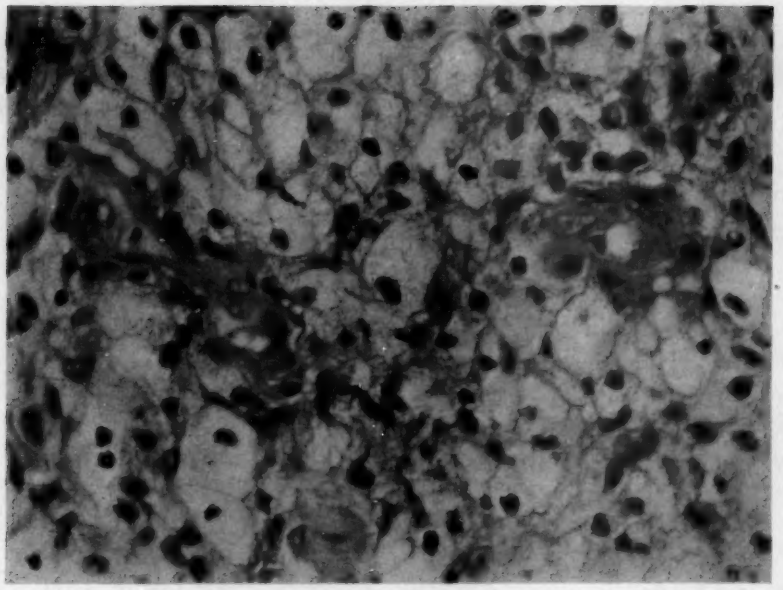

Fig. 1.—Chronic pelvic suppurative reaction showing foam cells. Hematoxylin and eosin stain; × 400 (A-81-33).

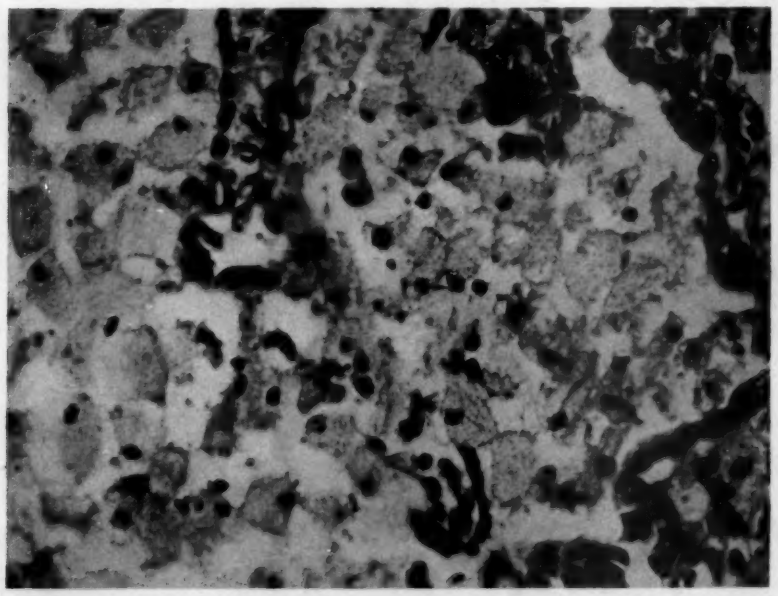

Fig. 2.—Section of lung (inhaled peanut with sequelae) showing foam cells in the alveoli. Hematoxylin and eosin stain; × 400 (A-387-32).

pale cells loaded with fatty substance, but not usually having the finely reticular character, as mentioned. It is also significant that cholesterol and its esters can rarely be demonstrated in these cells with the polarizing microscope. Extracellular fat and fibroblasts containing fat are found. In more advanced lesions of the superficial fatty streak variety, true foamy cells are frequently observed, and anisotropic fatty substances may be demonstrated.

In one case sections through the aorta revealed a remarkable picture. The intima was greatly thickened and greatly vascularized. Many capillaries were present, and surrounding these capillaries, in intimate relation to them, were large numbers of typical foam cells. The material studied was obtained during an autopsy (fig. 5) in a case in which thorotrast had been used clinically for diagnostic purposes. Thorotrast is a suspension of finely particulate thorium dioxide, and has been used recently as a method of outlining the reticulo-endothelial system (Irwin [22]), the cells of this system displaying an active phagocytic action toward particulate matter in the blood stream. It is significant and, I believe, an important finding that after a careful study thorotrast was found in small quantity within foam cells making up atheroma of the aorta. A few small, highly refractile particles were seen within typical foam cells surrounding the capillaries in the thickened intimal atheromatous plaque. The particles of thorium dioxide were usually to be seen at the periphery of the finely reticular cytoplasm and were demonstrated best in sections stained with hematoxylin and eosin and Masson's stain. The significance of this finding will be discussed later.

Foam cells may be seen in other conditions, and numerous authors have called attention to this fact (Haagensen,[23] Aschoff,[24] Harbitz [25] and Bloch [10]). Thus, in routine work several instances have been observed in a relatively short period. One example was found in connection with a chronic pelvic inflammation in which numerous small yellowish-orange nodules were found; on section of the nodules, fat stains and paraffin sections revealed the typical foam cells described, with a lipoid content similar to the xanthoma cell. Other examples were chronic abscess of the brain, chronic empyema and strawberry gallbladder. Another interesting case was that of a patient who died as a result of pneumonia following aspiration of a peanut several months previously. In this case sections of the lung presented the typical egg-yolk color in the gross; on microscopic examination, in many areas the alveoli were plugged with typical foam cells. The fat stains here again disclosed the lipoid content to be of a similar nature. In addition to those given,

22. Irwin, D. A.: Canad. M. A. J. **27**:130, 1932.

23. Haagensen, C. D.: Am. J. Cancer **16**:1077, 1932.

24. Aschoff, quoted by Brown, T. R., and Howard, J. T.: Internat. Clin. **4**: 106, 1931; quoted by Hoessli.[8]

25. Harbitz, F.: Arch. Path. **4**:507, 1927.

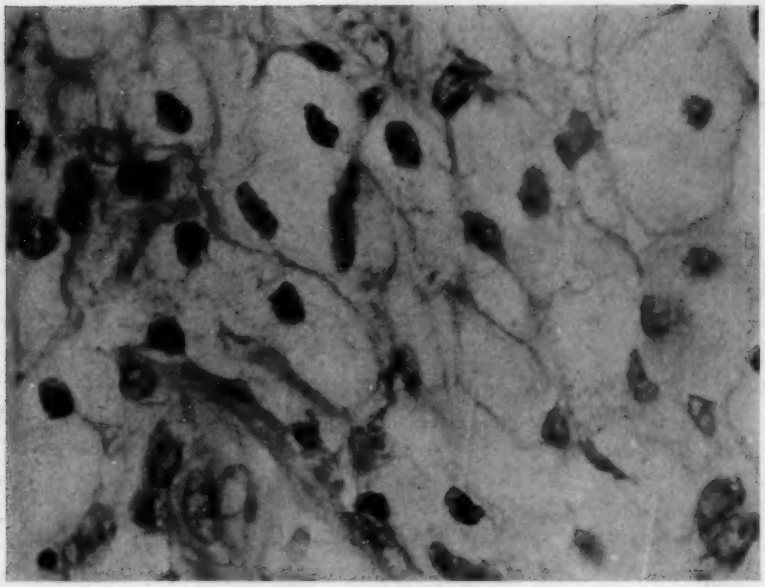

Fig. 3.—Xanthelasma palpebrarum, showing Touton giant cell and many foam cells. Hematoxylin and eosin stain; × 800 (U.S.C.-S-642-32).

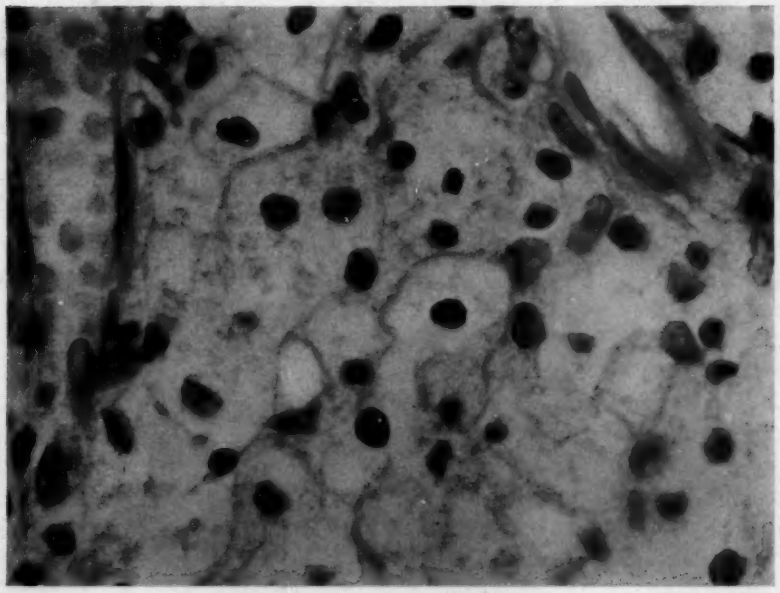

Fig. 4.—Xanthoma of the tendon sheath showing relation of the foam cells to the capillaries. Hematoxylin and eosin stain; × 800 (Dr. Bates T-888-31).

Stewart [26] listed the following conditions: cholesteatoma of the choroid plexus, myelin kidney, myeloid tumor of the tendon sheaths (endothelioma), subacute inflammation of the adipose tissue, subacute and chronic salpingitis, subacute and chronic abscesses, retention lesions of the breast, cerebral lesions in which there is degeneration of the myelin, dermoid cysts, mycosis fungoides, certain lesions of the thyroid gland and tumors showing degeneration. It will be seen that xanthoma and atheroma are found in cases with a probable derangement of cholesterol metabolism and are, therefore, generalized conditions. On the other hand, the remaining lesions are associated with a local degenerative

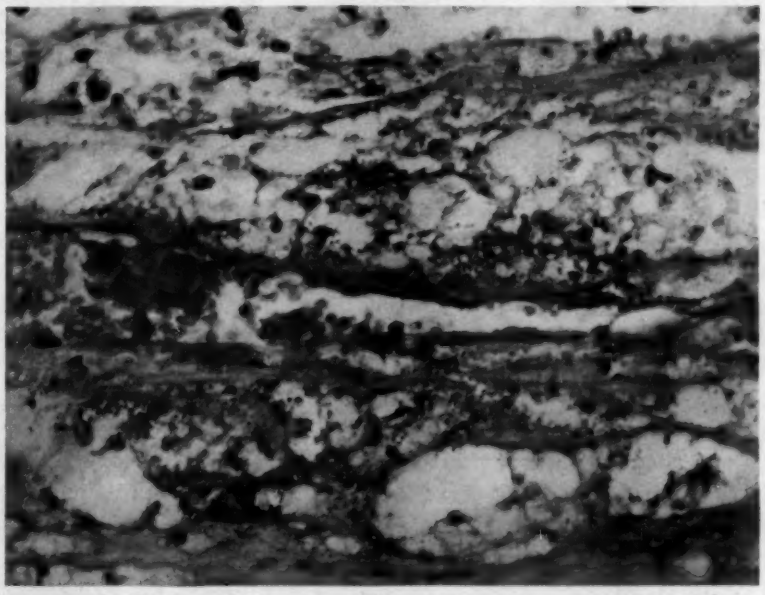

Fig. 5.—Aorta, showing vascularization of the intima with atheroma and foam cells containing thorotrast. Hematoxylin and eosin stain; × 400 (A-72-33).

process in which there is liberation of lipoid locally. Weber [27] added another case, one of arcus senilis, and in relation to all of these conditions, he spoke of a cholesterol diathesis.

Thus, it may be seen that certain types of lesions, characterized by a typical gross picture and consisting mainly of foam cells as seen under the microscope, are intimately linked together. On the one hand, there may be as an etiologic factor hypercholesteremia, or, again, an alteration in the lipoid constituents so that cholesterol is precipitated out. And, on the other hand, in certain other conditions in relation to chronic sup-

26. Stewart, M. J.: Brit. M. J. **2**:893, 1924.
27. Weber, F. P.: Brit. J. Dermat. **36**:335, 1924.

puration, a localized precipitation or infiltration of cholesterol esters occurs.[28] In all of these conditions foam cells may appear. Moreover, it is also noteworthy that in normal tissues not belonging to the reticulo-endothelial system, such as the lutein cells of the ovary, the cortex of the suprarenal glands and the sebaceous glands, cells with foamy cytoplasm are seen; this is related to a local increase in cholesterol in these tissues. I shall leave for the present consideration of Gaucher's disease and Niemann-Pick disease, since these conditions have been found to be associated with lipoids other than cholesterol.

When cholesterol is present in large amounts or when lipoid ratios are altered so that the cholesterol exists as finely particulate matter in colloidal suspension, it is phagocytosed by the cells of the reticulo-endothelial system. When these cells have performed this function, they gradually assume the form of the foam cell. What proof is there that the xanthoma cells are of the reticulo-endothelial system? By their very function of phagocytosis of particulate matter and colloidal material, they proclaim themselves as such. Moreover, Anitschow,[17a] in his experimentally produced xanthoma, found that the cells which phagocytosed the lipoid material picked up vital dyes. In a similar manner, I have demonstrated thorotrast, which is comparable to a vital dye in this regard, within foam cells in atheroma of the aorta. Thus I have shown not only that the foam cell of atheroma is probably identical in function to the xanthoma cell, but also that both probably arise from the same system of cells, that is, the reticulo-endothelial system. That lipoids other than cholesterol may act in this manner is demonstrated in the more rare diseases, Gaucher's disease and Niemann-Pick disease, the former being associated with a lipoprotein and the latter with a phosphatide.[29]

CONCLUSIONS

A series of eighteen cases of xanthoma, in which the nodules were removed surgically, was studied from a standpoint of the origin and nature of the xanthoma cell.

A study of fatty lesions of the arteries was made in relation to a fundamental similarity of atheroma and xanthoma.

It is believed that the xanthoma cell and the foam cell of atheroma, of chronic suppurative reactions and of certain systemic diseases are of identical nature.

Furthermore, I believe that the origin of both of these cells is from the reticulo-endothelial system, and that the foam cell is an evidence of specific reaction of the cells of the reticulo-endothelial system to certain lipoids, especially cholesterol and its esters, when conditions favorable for their deposition in tissues are present.

28. Landois, F., and Reid, M.: Beitr. z. klin. Chir. **95**:56, 1914.
29. Sosman, M. C.: Am. J. Roentgenol. **23**:581, 1930.

MULTIPLE NECROSES OF THE SPLEEN (FLECKED SPLEEN OF FEITIS)

WITH SPECIAL REFERENCE TO THE ASSOCIATED RENAL LESIONS

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In 1921, Feitis [1] reported a thorough study of two cases of multiple anemic necroses of the spleen which differed in both gross and microscopic structure from the forms described previously. The rarity of this condition is apparent, as only twenty-one cases have been described in the literature since Feitis' publication. These are briefly outlined in table 1.

The appearance of the spleen is characteristic. The cut surface shows many well defined, light yellow to gray-white areas which are firm and vary in diameter from 2 or 3 mm. to 2 cm. Frequently they are crowded closely to the peripheral portion of the spleen and are absent in the center, although in some cases the entire organ is involved. These areas are very irregular and of bizarre shape and frequently show jagged outlines. Many of the larger foci are connected by narrow bands of necrotic tissue, giving the surface a mosaic structure. These light-colored areas stand out conspicuously against the dark red-brown pulp. A distinct peripheral zone of hyperemia may be present around many of the necrotic areas. In some areas this is lacking. The organ occasionally shows marked atrophy. In most cases the spleen is of normal size, and in a few cases its weight is increased (Nicod; [2] Meuret,[3] case 2; Adolphs,[4] case 2).

On microscopic examination Feitis [1] distinguished two types of necrosis: (1) typical necrosis and (2) atypical necrosis. The typical necrosis conforms somewhat to the structure of an infarct, in that three zones are distinguishable: a necrotic central area composed of a structureless, dense mass of nuclear débris and necrotic parenchyma; a paler intermediate zone, or *Auslaugungszone,* containing necrotic parenchyma infiltrated with a few leukocytes, and a peripheral hemorrhagic zone which merges with the non-necrotic parenchyma. These areas are most numer-

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1. Feitis, H.: Beitr. z. path. Anat. u. z. allg. Path. **68**:297, 1921
2. Nicod, J. L.: Ann. d'anat. path. **7**:67, 1930.
3. Meuret, W.: Beitr. z. path. Anat. u. z. allg. Path. **73**:535, 1924.
4. Adolphs, E.: Frankfurt. Ztschr. f. Path. **41**:433, 1931.

TABLE 1.—*Cases of Flecked Spleen Found in the Literature*

Author	Sex; Age, Years	Size of Heart	Blood Pressure: Systolic	Blood Pressure: Diastolic	Cause of Death	Renal Changes	Appearance of Spleen
Feitis, 1921 Case 1	39	870 Gm.	240	...	Uremia	"Genuine contracted kidney" (arteriolosclerosis)	Weight, 205 Gm.; discrete and confluent irregular areas of anemic necrosis; degeneration of small and medium-sized arteries with occlusion; arteriosclerosis and thrombosis of larger arteries
Feitis, 1921 Case 2	Male 60	Marked hypertrophy of left ventricle	...	...	Uremia	"Horseshoe kidney with granular atrophy"	Atrophy; granular surface; large areas of necrosis beneath capsule; microscopic changes similar to those in case 1
Meuret, 1924 Case 1	31	Marked hypertrophy	...	...	Uremia	"Nephrosclerosis arteriolosclerotica"	Infarct-like areas replacing one third of spleen; obliteration of small arteries; secondary thrombosis of larger arteries
Meuret, 1924 Case 2	46	Hypertrophy and dilatation	200	...	Cerebral hemorrhage	"Hydronephrosis left; malignant nephrosclerosis right;" infarcts	Enlarged, firm and maculated; hyperplastic intimal changes in larger arteries; necrosis and occlusion of small arteries
Lubarsch, 1926 Case 1	..	Marked hypertrophy of left ventricle	...	...	Cardiac failure	"Contracted kidneys and uric acid deposits"	Weight, 215 Gm.; numerous areas of anemic necrosis; necrotic changes in small arteries; thrombosis and inflammation of larger arteries
Lubarsch, 1926 Case 2	Female 44	Marked hypertrophy of left ventricle	...	...	Cardiac failure	"Marked granular atrophy of both kidneys"	Small and indurated; fresh areas of anemic necrosis; arterial changes similar to those in case 1
Lubarsch, 1926 Case 3	Male 52	795 Gm.; hypertrophy of left ventricle	...	...	Cardiac failure	"Granular atrophy"	Weight, 130 Gm.; small areas of necrosis connected by strands; arterial changes as in case 1
Lubarsch, 1926 Case 4	Male 53	.....	...	...	Chronic uremia	"Atrophy of both kidneys"	Almost complete anemic necrosis due in part to arterial emboli and in part to arterial changes similar to those in case 1
Hosoi, 1928	Female 45	Clinically enlarged	230	140	Cerebral hemorrhage	"Chronic vascular nephritis"	Weight, 110 Gm.; irregular nodular maplike yellow areas; arterioles obliterated; fresh thrombosis of larger arteries

Kabakaris, 1930	Male 38	Marked hypertrophy of left ventricle	210	150	Uremia	Marked atrophy; chronic glomerulonephritis; arteriolosclerosis	Large; many discrete and confluent areas of necrosis; necrosis and occlusion of small and medium-sized arteries
Nicod, 1930	Female 48	500 Gm.; hypertrophy of left ventricle	250	180	Uremia	Moderate atrophy; "chronic glomerulonephritis; arteriolosclerosis"	Weight, 250 Gm.; firm, small yellow areas beneath capsule; proliferative intimal changes and hyalinization of small arteries
Klemperer and Otani, 1931	Female 46	Hypertrophy of both ventricles	210	135	Uremia; cardiac failure	Atrophy; "malignant nephrosclerosis"	Firm and nodular; mosaic in appearance due to multiple areas of necrosis
Adolphs, 1931 Case 1	Female 53	Hypertrophy	250	...	Cerebral hemorrhage	"Chronic glomerulonephritis with arteriolonecrosis"	Surface smooth; irregular pointed areas of necrosis beneath capsule and in center; necrotic changes in small and medium-sized arteries
Adolphs, 1931 Case 2	Male 57	Hypertrophy	...	...	Hemorrhage from ulcer	"Chronic glomerulonephritis," arteriolonecrosis and endarteritis	Enlarged; many irregular yellow areas of necrosis, more numerous in center; vascular changes similar to those in case 1
Adolphs, 1931 Case 3	Female 11	Dilatation	...	...	Uremia	"Early acute glomerulonephritis;" necrosis of vasa afferentia	Gray-yellow areas of necrosis in center; necrosis and occlusion of small arteries
Spier, 1931	Female 51	540 Gm.	...	...	Apoplexy	"Arteriolosclerosis"	Weight, 92 Gm.; multiple areas of necrosis beneath capsule; necrosis and occlusion of lumen of small arteries
Rake Case 1	Female 44	Hypertrophy of left ventricle	...	...	Uremia	"Arteriolosclerosis and arteriolonecrosis"	Weight, 140 Gm.; multiple infarct-like areas; occlusion of small arteries due to necrosis and thrombosis
Rake Case 2	Female 52	.....	...	...	Uremia	"Malignant nephrosclerosis"	Changes similar to those in case 1, except that degenerative arterial changes are more marked
Geipel, 1925	Female 35	.....	...	...	Eclampsia	"Multiple necrosis"	Weight, 330 Gm.; multiple yellow, confluent areas of necrosis throughout spleen; fibrinous thrombi occluding small arteries
Laufer, 1933 Case 1	Male 58	.....	...	...	.....	"Subacute-chronic glomerulonephritis"	Size, 13 by 7.5 by 5 cm.; multiple irregular areas of necrosis; acute endarteritis and periarteritis
Laufer, 1933 Case 2	Male 37	Hypertrophy of left ventricle	...	...	Uremia	"Chronic glomerulonephritis"	Size, 15 by 8.5 by 4.5 cm.; appearance of spleen and vascular changes similar to case 1

ous near the capsule. The areas of atypical necrosis are smaller and less frequently seen than the typical forms. They do not possess the three zones just described and vary considerably in structure. Large areas of necrosis are formed by the fusion of a number of smaller areas. There is no relation between the lymphoid follicles, trabeculae and pulp and the necrotic areas.

The vascular changes are pronounced, being most marked in the small and medium-sized central arteries of the follicles. In the majority of cases reported, these changes consist of necrosis of the wall which begins in the intima and extends into the media, causing confluence of these two layers. The walls are converted into a hyaline coagulated mass containing scattered nuclear fragments. In many of these vessels the endothelium is destroyed and the lumen is filled with a hyaline substance which merges with the necrotic walls of the vessel. Marked hyperplastic elastic intimal thickening and regenerative connective tissue proliferation of the intima are present in the larger vessels of the trabeculae. Occasionally, these vessels contain partially organized thrombi. With the exception of one case (Lubarsch,[5] case 4) embolic phenomena have been absent. The veins are not affected primarily.

Geipel [6] reported a case of puerperal eclampsia in which splenic changes similar to those described by Feitis [1] were noted. These changes were associated with multiple necroses of the cortex of the kidneys. The vascular changes in this case differed from those described in the other cases cited. The small arteries of the red pulp, the central arteries of the lymphoid follicles and a few of the small trabecular arteries were partially or completely occluded by fibrin thrombi. The peculiar necrosis of the arterial walls seen in other cases of flecked spleen was lacking in Geipel's case. The larger arteries were not affected. Mathias, in a discussion of Geipel's [6] paper, stated that he had seen similar changes in the spleen of an eclamptic patient showing the typical changes in the liver described by Schmorl. This case is not included in table 1, since no description is given. Mathias expressed the opinion that the necrosis was due to angiospasm followed by endothelial injury and thrombosis. Lubarsch [5] maintained that in these cases the thrombosis and subsequent necrosis are due to a toxic factor, and he accordingly designated this condition as the "toxic-thrombotic" form of flecked spleen, in contradistinction to the type described by Feitis,[1] Meuret [3] and others, which

5. Lubarsch, O.: Pathologische Anatomie der Milz, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histology, Berlin, Julius Springer, 1927, vol. 1.

6. Geipel: Centralbl. f. allg. Path. u. path. Anat. **35**:8, 1924; Arch. f. Gynäk. **124**:231, 1925.

he classed as "arteriosclerotic autotoxic" flecked spleen. Hosoi [7] adopted a similar classification but incorrectly included in the toxic-thrombotic group a case of pernicious anemia described by Lubarsch [5] in which multiple necroses of the spleen occurred following blood transfusion. In this case thrombosis was completely lacking, and for this reason Lubarsch hesitated to include it in the toxic-thrombotic group or to classify it as a form of flecked spleen. As a toxic cause of thrombosis of the small arteries in eclampsia and the pathogenesis of arteriolonecrosis are still disputed, a classification of flecked spleen based on etiologic pathologic information is not justifiable. It would be less confusing to regard the type of lesion described by Geipel as a thrombotic form of flecked spleen, as distinguished from the arteriosclerotic form described by Feitis and others.

The existence of a third, or arteritic, type of flecked spleen is indicated by the recent case reports of Laufer.[8] The lesion is inflammatory, involving the small and medium-sized arteries of the spleen. Laufer found marked leukocytic infiltration of the adventitia and media, frequently with necrosis and swelling of the media and connective tissue proliferation of the intima. Laufer classified the lesion as periarteritis nodosa. The vascular changes, however, do not conform entirely to the classic picture of periarteritis nodosa described by Kussmaul and Maier,[9] since the arteries of visible caliber are not involved, aneurysmal dilatations are not described and thrombosis is lacking. Moreover, the areas of anemic necrosis of the spleen do not resemble the infarct-like lesions found in classic cases of periarteritis nodosa. The type of vascular lesion described by Laufer is similar to that seen occasionally in cases of subacute glomerulonephritis (Klemperer and Otani [10]) and in cases of malignant hypertension (Fahr [11]). Klemperer designated these lesions as necrotizing arteritis, endarteritis and periarteritis, as distinguished from the purely degenerative vascular type, or arteriolonecrosis, seen in most cases of malignant hypertension.

Enzer,[12] in 1926, described a case of multiple necroses of the malpighian bodies in a case of pernicious anemia. Death was due to bronchopneumonia. Although Enzer included the case as a typical

7. Hosoi, K.: Arch. Path. **6**:26, 1928.

8. Laufer, S.: Centralbl. f. allg. Path. u. path. Anat. **58**:113, 1933.

9. Kussmaul and Maier, quoted by Jores, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1924, vol. 2.

10. Klemperer, P., and Otani, S.: Arch. Path. **11**:60, 1931.

11. Fahr, T.: Pathologische Anatomie des Morbus Brightii, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1925, vol. 6, pt. 1.

12. Enzer, N.: Am. J. Path. **2**:511, 1926.

example of flecked spleen, differing only in etiology, there seems to be meager evidence for this assumption. The large, irregular, connected areas of necrosis, easily visible to the naked eye, found in all the cases reported in table 1, were not present in Enzer's case, the necrotic areas being extremely small and barely visible to the naked eye. There were no evidences of vascular disease, such as obliteration of the lumens or the formation of thrombi. There is little ground for Enzer's assumption that flecked spleen of Feitis is characterized by necrosis of the malpighian bodies. No description of this is given in the papers of Feitis,[1] Lubarsch,[5] Meuret,[3] Adolphs,[4] and others. Feitis stated that no relationship could be found between the areas of necrosis and the malpighian bodies. In many of the cases, the lymphoid tissue is very scant and consists of narrow cylindric sheaths about the central arteries. Feitis [1] was unable to find changes other than fibrosis and occasionally hyalinization of the lymphoid tissue. When the follicles are included in the areas of necrosis, their cellular structures appear much better preserved than other structures about them.

The splenic changes described by Enzer in all probability belong to the group of infectious toxic necrosis not infrequently seen in various infectious diseases, such as typhus, acute and subacute endocarditis, scarlet fever and diphtheria. It resembles particularly the changes sometimes seen in scarlet fever and diphtheria, in which the necrosis is limited to the malpighian corpuscles.

Wilton's [13] case and case 3 of Lauber [8] are somewhat similar to the one reported by Enzer. In Wilton's case, the spleen was considerably enlarged and beset with numerous small white areas and a few large irregular foci resembling somewhat the picture seen in tuberculous caseative necrosis and abscess formation involving the malpighian bodies. The central arteries of the follicles in the region of the necrotic areas were thrombosed. The thrombosis was secondary to the perivascular necrosis. Wilton believed that there was marked similarity between this case and that described by Feitis. Lubarsch,[5] however, was inclined to the view that the two conditions are different. It is more likely that, as in Enzer's case, the condition described by Wilton is a type of necrosis and multiple abscess formation of the malpighian bodies encountered in various infectious diseases. Lauder's case 3 similarly was associated with streptococcic septicemia in which multiple abscesses, infarct-like lesions and acute arteritis with thrombosis were noted.

CHANGES IN THE KIDNEYS

The interpretation of the renal lesions in the cases of flecked spleen described in the literature offers considerable difficulty, especially in those

13. Wilton, A.: Frankfurt. Ztschr. f. Path. **31**:110, 1925.

cases in which a detailed microscopic picture is not given. The renal condition, with few exceptions, is associated with essential hypertension and uremia. The diagnosis is extremely varied, as noted in table 1. Such terms as arteriolosclerosis, malignant hypertension, vascular nephritis, nephrosclerosis arteriosclerotica, granular atrophy and chronic glomerulonephritis with arteriolonecrosis are used to indicate identical or closely related conditions. This disagreement in terminology is readily understood since there is still little agreement, especially among pathologists, as to the exact nature of the renal disease in essential hypertension.

Volhard and Fahr,[14] in 1914, stated that hypertension with renal insufficiency differs in its pathogenesis from the form without renal insufficiency, or benign hypertension. The former, termed *Kombinationsform,* was thought to be due to a combination of arteriosclerosis with inflammatory renal changes. Since that time, these authors have modified their views. Volhard [15] has ceased to believe that the presence of inflammatory glomerular changes distinguishes the combination form from benign arteriosclerosis; he has come to feel that the difference is quantitative, both conditions resulting from ischemia following vascular spasm. Fahr [11] has recognized the fact that renal insufficiency may occur as a slow process during the course of benign sclerosis. Accordingly, he divided the renal changes in essential hypertension into three types: (1) compensated benign sclerosis (pure arteriosclerotic kidney in the stage of compensation); (2) decompensated benign nephrosclerosis, and (3) malignant (specific) nephrosclerosis. He expressed the belief that malignant sclerosis differs from the other forms both pathogenically and histologically. In the malignant form, inflammatory vascular changes in the form of necrotizing arteriolitis, productive endarteritis and periarteritis are present. These lesions are due to a specific toxic factor which is absent in the other forms of hypertensive renal disease.

The separation of the diseases into two distinct pathologic types by Fahr is not accepted by many observers. Löhlein [16] maintained that there is no essential anatomic difference between the two forms. Klemperer and Otani [10] held that malignant hypertension represents an acute and accelerated form of atherosclerosis in which the etiologic agent is the same. Bell and Clawson [17] similarly objected to Fahr's classification and denied the existence of a separate pathogenic form. They divided primary hypertension with renal insufficiency into three types: (1) acute

14. Volhard, F., and Fahr, T.: Die Brightsche Nierenkrankheit, Berlin, Julius Springer, 1914.

15. Volhard, F., quoted by Klemperer and Otani: Arch. Path. **11**:60, 1931.

16. Löhlein, M.: Centralbl. f. allg. Path. u. path. Anat. **28**:209, 1917.

17. Bell, E. T., and Clawson, B. J.: Arch. Path. **5**:939, 1928.

hypertension with uremia; (2) chronic hypertension ending acutely in uremia, and (3) chronic hypertension with chronic uremia. The third form is the most common. The renal insufficiency is due to gradual atrophy and fibrosis of the parenchyma following slow vascular occlusion. The first and second forms are frequently associated with necrosis of the arterioles leading to rapid occlusion of the lumens of the arterioles and at times to infarction of the glomeruli. This classification is the most satisfactory because it does not assume an etiologic difference between the three forms and avoids the term malignant hypertension which may be justifiably applied to either the first or the second type.

In all instances of the arteriosclerotic form of flecked spleen in which a fairly complete description of the kidneys was recorded, marked degenerative changes have been noted in the arterioles. These changes infrequently consist only of marked hyaline deposits in the intima, but most of the cases show in addition marked necrosis of the arterioles. These changes are similar to those seen in the small arteries of the splenic follicles; they consist of necrosis of the intima and media, loss of endothelium, hemorrhagic infiltration of the walls and occlusion of the lumen with a hyaline substance. The changes in the larger vessels are arteriosclerotic and consist principally of hyperplastic elastic intimal thickening and connective tissue proliferation.

The glomerular changes are varied in nature. In most cases the glomeruli appear small and frequently show from partial to complete hyalinization. Epithelial and endothelial proliferation has been described in a few instances. Necrosis of portions or of the whole of the glomeruli is noted. This is due to occlusion of the vasa afferentia.

Because of the marked atrophy of the kidneys, it is apparent that many of these cases fall into the second type of Bell's classification, i. e., chronic hypertension ending acutely in uremia. These include the cases described by Lubarsch, Rake [18] (case 1), Feitis [1] (case 1) and Meuret [3] (case 1). A few cases fit more closely into Bell's first type, or acute hypertension with uremia (malignant hypertension of Fahr; accelerated atherosclerosis of Klemperer). The cases of Klemperer,[10] Rake [18] (case 2) and Adolphs [4] (case 3) probably belong to this group. Many cases, however, cannot be classified in either of these groups since anatomic descriptions of the kidneys are lacking.

In six instances, a diagnosis of chronic glomerulonephritis is recorded (Laufer [8] [cases 1 and 2], Kabakaris,[19] Nicod [2] and Adolphs [4] [cases 1 and 2]). Lauder's cases lack evidence of arteriosclerosis and

18. Rake, G.: Am. J. Path. **18**:107, 1932.

19. Kabakaris: Contribution à l'étude des nécroses de la rate au cours de l'urémie, Thèse de Lausanne, 1930; quoted by Nicod: Ann. d'anat. path. **7**:67, 1930.

appear to be examples of subacute and chronic glomerulonephritis showing acute inflammatory vascular lesions resembling periarteritis nodosa. In the other cases, marked vascular lesions consisting of atherosclerosis of the larger vessels, arteriosclerosis and arteriolonecrosis similar to that described were noted. Adolphs, although including chronic recurrent glomerulonephritis in the anatomic diagnosis, stated in the discussion that the renal alterations in his cases 1 and 2 were similar to those described by Fahr [11] in malignant sclerosis and by Stern [20] and Herxheimer [21] in arteriolonecrosis.

The differential pathologic diagnosis between borderline cases of chronic glomerulonephritis and of essential hypertension with uremia is exceedingly difficult. It has been pointed out by Fahr [11] Klemperer and Otani,[10] McGregor [22] and Bell and Clawson [17] that frequently in cases of essential hypertension with uremia inflammatory changes are seen which are indistinguishable from those occurring in glomerulonephritis, varying only in degree of involvement. Crescent formation, proliferation of glomerular endothelium, fusion of tufts of the glomeruli and leukocytic infiltration are frequently seen. Bell expressed the belief that these changes are due to a superimposed inflammatory process. Klemperer and Otani, however, stated that they are due to ischemia following occlusion of the arterioles. On the other hand, in long-standing chronic glomerulonephritis in which the hypertension is severe, changes may occur in the arteries of the kidneys which are indistinguishable from those occurring in hypertension with uremia. Differentiation between the two conditions is based on the prominence of vascular lesions or the inflammatory glomerular lesions; the former are marked in essential hypertension, whereas the latter are more marked and more diffuse in chronic glomerulonephritis. However, there are occasionally borderline cases which are difficult to classify, and not infrequently a subjective element enters into the interpretation of these lesions.

The clinical features in the cases of flecked spleen reported by Adolphs,[4] Nicod [2] and Kabakaris [19] correspond closely to the picture of essential hypertension, since in all cases marked cardiac hypertrophy was observed and the blood pressure was above that usually seen in chronic glomerulonephritis (Nicod, 250 systolic and 180 diastolic; Kabakaris, 210 systolic and 130 diastolic; Adolphs [case 1], 250 systolic). Cerebral hemorrhage, which occurred in Adolph's case is rare in chronic glomerulonephritis, whereas it is commonly observed as a cause of death in essential hypertension.

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20. Stern, M.: Virchows Arch. f. path. Anat. **251**:718, 1924.
21. Herxheimer, G.: Virchows Arch. f. path. Anat. **251**:709, 1924.
22. McGregor, L.: Am. J. Path. **6**:347, 1930.

For these reasons it seems probable that the cases of Kabakaris, Nicod and Adolphs are examples of essential hypertension with marked vascular changes leading to an inflammatory glomerular reaction rather than cases of chronic glomerulonephritis.

Adolphs' case 3 also presents difficulty in classification. The disease lasted only 10 days and terminated in uremia. A diagnosis of early acute diffuse glomerulonephritis was made on the basis of marked diffuse glomerular inflammation. There was also a marked vascular lesion in the form of necrosis and occlusion of the vasa afferentia. Adolphs expressed the belief that the condition was identical with that in the case of early acute glomerulonephritis described by Kuczunski and Hückel, but he admitted that because of the marked arteriolonecrosis it is difficult to differentiate this condition clearly from acute hypertension with uremia.

TABLE 2.—*Age of Patients with "Malignant and Benign Sclerosis" (from Klemperer and Otani) Compared with Age of Patients with the Arteriosclerotic Form of Flecked Spleen*

Age, Years	Malignant Sclerosis		Benign Sclerosis		Flecked Spleen	
0–10	1		0		0	
11–20	0		0		1	
21–30	4	75%	0	29%	0	66.6%
31–40	3		4		4	
41–50	4		14		7	
51–60	4		16		6	
61–70	0	25%	22	71%	0	33.3%
71–80	0		6		0	
Total	16		62		18	

The age incidence in eighteen cases of the arteriosclerotic type of flecked spleen, when compared with that for malignant sclerosis and benign sclerosis obtained from the studies of Klemperer and Otani (table 2), lends further support to the fact that the renal lesions associated with the arteriosclerotic type of flecked spleen are similar to those in the cases included under the term "malignant or accelerated atherosclerosis." The age distribution of the cases of flecked spleen parallels closely that for malignant sclerosis; 66.6 per cent of the former and 75 per cent of the latter occurred before the sixth decade of life, whereas, 71 per cent of the cases of benign sclerosis occurred in the sixth, seventh and eighth decades.

REPORT OF A CASE

History and Course.—A woman, aged 45, entered the Colorado General Hospital on Feb. 24, 1933, complaining of progressive weakness and the loss of 40 pounds (18.1 Kg.) in two months. In December, 1932, she contracted a cold which confined her to bed. Since the onset of the cold she had had nocturia and pain in the region of the kidneys. Swelling of the feet and ankles occurred on standing.

The fundi oculi showed star-shaped exudate about the maculae, papilledema and hemorrhage. The heart was enlarged. The blood pressure was 232 systolic and 128 diastolic. The blood chemistry on Feb. 27, 1933, showed: nonprotein nitrogen, 192 mg.; urea nitrogen, 152 mg., and creatinine, 12 mg. On March 29, the nonprotein nitrogen was 324 mg., and the urea nitrogen, 256 mg. Hemoglobin was 50 per cent (Dare); the red blood cell count was 2,410,000, and the white cell count, 17,000. Urinalysis showed: specific gravity, 1.010; albumin, 3 plus, and many granular casts and white blood cells. The phenolsulphonphthalein test showed no dye recovered. The Wassermann test was negative.

Ulcerative stomatitis developed and the patient died on March 30, 1933.

Necropsy.—The anatomic diagnosis was: arteriosclerosis and arteriolonecrosis of the kidneys; bronchopneumonia; hypertrophy of the heart, especially of the left ventricle; arteriolonecrosis of the heart, suprarenals, pancreas and spleen; serofibrinous pericarditis; ulcerative stomatitis; multiple necroses of the spleen; interstitial fibrosis of the pancreas; generalized atherosclerosis.

The body was poorly nourished; the weight was 90 pounds (40.8 Kg.), and the length, 164 cm. There were areas of ulceration of the buccal and gingival mucous membrane. The heart weighed 595 Gm. There were moderate dilatation and hypertrophy of the right ventricle and marked hypertrophy of the left ventricle. There was a serofibrinous exudate in the pericardial sac. The proximal portion of the anterior descending branch of the left coronary artery showed marked atheromatous deposits and calcification, causing marked reduction in the size of the lumen. The aorta showed a marked degree of atherosclerosis, especially in the lower abdominal portion. The lower lobes of both lungs showed bronchopneumonic consolidation.

The spleen weighed 40 Gm. The capsule showed a moderate degree of hyaline thickening. The surface was roughly nodular. The splenic artery was rigid and tortuous. Its lumen was widely patent. No changes were noted in the splenic vein. The cut surface of the spleen showed many firm, light yellow areas, which stood out in marked contrast to the dark brown-red pulp. They were located, for the most part, near the capsule, the central portion of the spleen being comparatively free. A few of these areas were roughly wedge-shaped; others were irregular, with pointed processes, and a few were small and circular. They varied in diameter from about 2 mm. to 1.5 cm. The larger areas were often connected by narrow bands of light yellow tissue. A zone of hyperemia was noted about some of the larger nodules. The rest of the spleen was firm. The trabeculae appeared increased in thickness.

Both kidneys were shrunken; the left weighed 80 Gm., and the right, 75 Gm. The capsule was firmly adherent to the cortex in places. The surface was finely granular. A few deep depressions were present. There were many small cysts near the surface. The cortex was pale gray-brown. It was markedly reduced in thickness. The renal arteries were rigid and thick-walled.

Microscopic Examination.—Spleen: (*a*) Appearance of the Non-Necrotic Tissue. The trabeculae and the capsule were markedly thickened. The elastic fibers were increased in number and thickness, especially in the trabeculae. The outer portion of the capsule contained few elastic fibers but an abundance of thick collagenous fibers. In places there were small foci of lymphocytes among the collagenous fibers of the capsule and beneath the serous surface. The lymphoid tissue about the central arteries was somewhat diminished in amount. Secondary follicles were absent. The lymphocytes were well preserved and showed no evidence of degeneration. The reticulum of the white pulp appeared thicker and

more compact than normally. The reticular fibers of the red pulp were much coarser and denser than normally. Large numbers of macrophages loaded with hemosiderin were present in the pulp cords and in the sinuses. These cells were irregular in distribution, being closely packed in some areas and few in number in other areas. They bore no relation to the areas of necrosis. In places the venous sinuses were widely patent and distended with red blood cells. In other areas they were small and bloodless.

Fig. 1.—A low power photomicrograph through several necrotic foci in the spleen, showing (*a*) the central zone of necrosis, (*b*) the intermediate zone and (*c*) the peripheral zone of hyperemia. Marked arteriosclerotic thickening of the large vessels of the trabeculae is also shown.

(*b*) Areas of Necrosis. The size and structure of these areas varied considerably. The larger necrotic masses usually showed three fairly well defined zones (fig. 1). Centrally, and occasionally eccentrically, there was a well defined zone consisting of a densely packed mass of degenerated nuclei showing many stages of pyknosis and karyorrhexis. Many of these cells had lobulated nuclei and resembled polymorphonuclear leukocytes. The oxidase stain showed that this zone was loaded with blue-staining granules arranged in irregular small clusters and scat-

tered globules, some of which were from 2 to 3 microns in diameter. This granular mass was embedded in a coarsely reticulated structure which stained light blue with hematoxylin-eosin, light red with Mallory's aniline blue and pale yellow with van Gieson's stain. With Foot's modification of Hortega's silver carbonate method for reticulum [23] a few scattered reticular fibers were found, which were fragmented and thickened and stained poorly. At the periphery of this zone, the necrotic elements were grouped close together and contained clumps of amorphous débris which took a deep red-violet stain with hematoxylin-eosin. Peripheral to this zone there was a rather distinct area of necrosis which varied in thickness. It consisted, for the most part, of a homogeneous mass of necrotic tissue staining less heavily than the central zone and containing fewer and more scattered fragments of nuclei. Included in this mass were fragments of trabeculae, blood vessels and lymph follicles, the outlines of which were fairly distinct. With aniline blue a framework of thick, pale blue-staining fibers could be made out. With scarlet red, there was an abundance of fat in the form of small isolated droplets and small clusters of droplets of irregular size. Fat was much more abundant in this zone than in the central zone. The third, or peripheral, zone was an area of hyperemia which merged gradually into the intermediate zone. The inner portion contained many polymorphonuclear cells and large macrophages loaded with cellular débris. There was no evidence of connective tissue proliferation. With a stain for hemosiderin a few isolated granules were seen in the central and intermediate zones, and many coarse clusters in the peripheral zone. The oxidase stain (Schultze) showed fewer and more scattered granules in the intermediate zone than in the central zone. The peripheral zone contained numerous cells giving the oxidase reaction. Some of the larger areas of necrosis were composed of conglomerate clusters of smaller areas, since some of them showed two or more central zones.

In addition to these areas of necrosis, there were many small necrotic areas which did not show the three zones described. Some areas showed a structure similar to that of the central zone surrounded by an area of hyperemia. Other areas showed early necrosis of the parenchyma, with a diffuse infiltration of polymorphonuclear leukocytes. Small foci of early necrosis of the parenchyma showing little or no cellular reaction were present. These areas bore no relation to the trabeculae or to the lymphoid elements.

(*c*) Changes in the Arteries. The small central arteries of the white pulp showed striking changes, especially near the areas of necrosis. Replacing the intima and a large portion of the media, there was a dense layer of a homogeneous substance staining a light pink-lavender with hematoxylin-eosin. This amorphous material was sometimes arranged in the form of irregular wavy bands which were roughly parallel to the wall of the vessel. In many of these vessels the endothelium was lacking and the lumen was completely filled by a hyaline substance, embedded in which there were occasional deformed nuclei and red blood cells (fig. 2). With van Gieson's stain, this hyaline material was light yellow with orange streaks, and with Mallory's aniline blue, a homogeneous dark cloudy blue. Weigert's stain for fibrin failed to reveal a positive color reaction. With the elastic tissue stain, the inner elastic membrane appeared to be embedded in the hyaline substance, stained poorly and in many places was split into two or more indefinite layers. Many of the fibers were discontinuous and fragmented.

The precapillary arteries of the red pulp occasionally showed changes which were similar to those of the arteries in the white pulp. Many of these vessels were converted into a hyaline mass containing nuclear fragments. This hyaline material

23. Foot, N. C., and Menard, M. C.: Arch. Path. **4**:211, 1927.

occluded the lumens of many of the arteries. However, these changes were not as widespread or as marked as the changes in the arteries of the follicles.

The large central arteries of the lymphoid sheath and the small arteries of the trabeculae also showed striking changes. Hyaline material similar to that seen in the smaller vessels was present in many of these arteries, involving the intima and the inner portion of the media and frequently occluding the lumen. Occasionally red blood cells and leukocytes were seen in the outer layers of these vessels. In addition to these changes, the arteries of the trabeculae showed a marked degree of atherosclerosis. There was marked connective tissue proliferation, causing marked diminution in the diameter of the lumen in many of the arteries. The inner elastic membrane was frequently thickened, and often it showed two or more layers. Heavy deposits of calcium were present in the intima and frequently in the media.

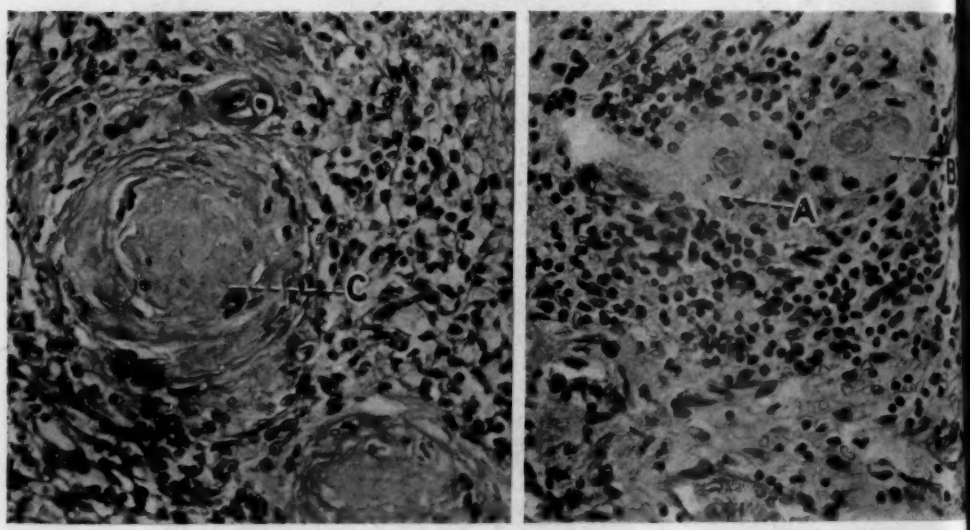

Fig. 2.—Necrosis of the inner wall of two small arteries (*A* and *B*) and one large artery (*C*) of the lymphoid follicle of the spleen. The lumens of these arteries are completely filled with a hyaline substance.

At times the calcium formed a complete thick ring in the wall of the artery. Calcification of the internal elastic membrane was seen. Some of the thickened, calcified vessels showed marked necrosis of the intima and media, with extravasation of blood between the necrotic layers and infiltration of polymorphonuclear cells. In the lumens of these vessels there were clumps of coarse granules which stained dark violet with hematoxylin-eosin and black with von Kossa's stain for calcium. In places, as the result of partial destruction of the inner wall of the vessels, the granular deposit in the lumen was continuous with the calcium deposits in the intima and media (fig. 3). About these granules were necrotic cells containing droplets of fat and red blood cells. A few of the vessels of the trabeculae showed partially organized thrombi occluding the lumen. With scarlet red, fat was abundant in the intima of the trabecular arteries which showed connective tissue hyperplasia of the intima. In many of the necrotic vessels of the follicles, small droplets of fat were seen in the amorphous hyaline material described.

In a few of the small veins, the lumen was partially closed by platelet thrombi. Most of the veins, however, appeared normal.

Kidneys: Many of the glomeruli were enlarged. Occasionally there was fusion of one or more tufts with the Bowman capsule. In some of the glomeruli, there was marked swelling as well as an increase in the number of endothelial cells and a moderate increase in polymorphonuclear leukocytes in the lumens of the capillaries. There was no evidence of crescent formation. With the azan-carmine aniline blue stain the basement membrane of the glomerular tufts appeared thickened and tortuous. Many of the loops contained intracapillary fibrils which formed a distinct network. In places, the capillaries were filled with a dense blue-staining

Fig. 3.—A trabecular artery, showing necrosis of the inner wall with extravasation of red blood cells and infiltration of leukocytes. There is desquamation of the necrotic tissue and calcium into the lumen of the vessel.

fibrillar material which completely occluded the lumen and was fused with the capillary basement membrane. Some of the glomeruli showed a moderately thickened capsular basement membrane. Some of the glomeruli showed necrosis of the tufts, and a few were converted into an amorphous granular mass containing necrotic nuclear fragments. Hyaline droplets were noted in many of the swollen endothelial cells. A large percentage of the glomeruli showed varying degrees of hyalinization.

The interlobular arteries showed marked thickening of the intima, owing to an increase in thickness and duplication of the internal elastic membrane and to connective tissue hyperplasia. There was a marked subintimal deposit of hyalin in the afferent arterioles, causing a marked diminution in the size of the lumen.

Other arterioles showed changes similar to those in the small arteries of the spleen, namely, marked necrosis of the walls with the formation of a hyaline material which frequently occluded the lumen. Embedded in the hyaline substance were fragmented nuclei. Scarlet red showed numerous fat droplets in the hyaline masses. There was no evidence of periarteritis or endarteritis. The tubules showed marked degenerative changes. Many of them contained large plugs of leukocytes. The cytoplasm of the convoluted tubules contained many hyaline droplets. Atrophy of the parenchyma was marked, with replacement by connective tissue containing many lymphocytes.

Pancreas: Many of the small arteries of the pancreas showed changes similar to those seen in the follicular arteries of the spleen. However, the lesions were not as severe or as extensive. There were occasional medium-sized arteries which showed marked atherosclerosis and degenerative changes similar to those seen in the spleen. A moderate degree of interstitial fibrosis was present.

Heart: There was replacement of areas of muscle bundles with hyalinized connective tissue. In the adventitia of many of the small arteries there was infiltration with polymorphonuclear cells and a few lymphocytes and plasma cells. An occasional small artery showed necrosis and hyalinization with occlusion of the lumen similar to the change seen in the spleen and kidneys.

Other Organs: In the capsule of the suprarenal glands, small arteries containing a thick hyaline band beneath the intima were occasionally seen. No changes were observed in the small vessels of the brain. Section through the lower lobes of the lungs showed early lobular pneumonia. The vessels of the lungs appeared normal.

COMMENT

The renal changes in this case correspond to the second type of Bell's classification, i. e., chronic essential hypertension terminating in acute uremia. Because of the marked cardiac hypertrophy and renal atrophy, it is justifiable to conclude that the hypertension had existed for a long time. The disease was not clinically manifest until about two months before death, following an acute infection of the upper respiratory tract. Symptoms of uremia and of albuminuric retinitis rapidly developed, and the patient died in uremic coma. The outstanding renal changes, in addition to the long-standing atherosclerosis, was marked necrosis of the vasa afferentia. Arteriolitis such as Fahr [11] observed in malignant hypertension was absent. The inflammatory lesions in the glomeruli were not diffuse but focal and consisted of changes which were similar to those seen in glomerulonephritis. Necrosis of the glomeruli due to closure of the vasa afferentia was also noted.

Symptoms referable to involvement of the spleen were lacking. Multiple infarct-like areas occupied about one third of the organ. The appearance of the spleen was similar to that described in case 2 of Feitis.[1] The marked irregularity in the shape of the necrotic foci was due to the confluence of small areas of necrosis. Because of this, the microscopic structure of these infarcts was more complex than that due to embolic occlusion of large vessels. Moreover, they differed from embolic infarctions in that most of the necrotic areas were heavily infil-

trated with leukocytes. This difference may be accounted for by the fact that in embolic infarction the large areas of anemic necrosis are produced by the closure of large arteries, whereas in flecked spleen the necrosis is due to the closure of many small arteries. Because of the richness of the collateral vascular supply about these small areas of infarction in flecked spleen, the degenerative changes, in all probability, proceed slowly and incite a marked response of polymorphonuclear leukocytes and macrophages. The larger areas, in which three well defined zones can be distinguished, were probably caused by occlusion of the larger arteries of the trabeculae. The vascular changes were similar to those seen in the kidneys, although more extensive. Two types of lesions were observed: (1) marked atherosclerosis of the medium-sized and large arteries of the trabeculae, with marked hyperplasia of the intimal elastic fibers and connective tissue hyperplasia, marked fatty degeneration and calcification; (2) necrosis of the trabecular arteries and especially of the arteries of the follicles, leading to occlusion of the lumens. In the medium-sized trabecular arteries were seen peculiar changes. There was marked necrosis of the walls, with desquamation of the inner wall into the lumen of the vessel. Because of the heavy calcium deposit and the atheromatous intimal changes, clumps of this material were seen occupying the lumens of many of these vessels. Spier [24] described this violet-staining material in the lumens, but he claimed that the substance is fatty, since it reacted positively to specific stains for fat. However, this material also took von Kossa's silver stain for calcium. On staining with scarlet red and counter-staining with methylthionine chloride, U. S. P. (methylene blue), an abundance of fat droplets was present in addition to a large amount of calcium which stained dark blue. In some of the arteries, the granules of calcium were still in direct contact with the heavy calcium deposits in the intima and media (fig. 3), indicating their origin from this source. Spier's view, that this material is not a form of thrombus but a product of degeneration of the wall of the vessel, was well taken. However, contrary to her observations and in accordance with those of Feitis, a few of the trabecular vessels showed thrombi which are partially organized.

The nature of the material occluding the smaller arteries is difficult to determine. It consisted of a homogeneous, amorphous substance, which stained light pink-violet with hematoxylin-eosin and which was arranged at times in the form of thick, irregular laminae lying parallel to the walls of the vessel. It stained dark blue with Mallory's aniline blue and pale yellow to orange with van Gieson's stain. Wright's fibrin stain and Mallory's aniline blue stain failed to show any evidence of fibrin. The marked similarity of this substance to the subintimal deposits

24. Spier, B.: Frankfurt. Ztschr. f. Path. **41**:160, 1931.

of hyalin commonly seen in these vessels strongly suggests a similar origin. The nature of this hyaline deposit is still not understood. Heuck [25] expressed the belief that it consists of coagulated albuminous substances. Whether it is in a fluid or a solid state has not been determined. It is conceivable that this hyaline substance may swell and accumulate rapidly in acute forms of hypertension and that following necrosis of the endothelial lining it may completely occlude the lumen of the vessel.

Feitis [1] considered three possibilities in an attempt to account for the peculiar necrosis of the spleen: (1) that the necrosis is due directly to occlusion of the smaller and medium-sized arteries; (2) that the changes are due to a combination of two factors, a toxic injury to the parenchyma and partial or complete occlusion of the arteries, and (3) that the lesion is due to toxic injury of the parenchyma, the vascular changes being secondary. He concluded that the first theory is the most plausible.

It is evident that in the case reported here the lesions in the arterioles and the larger arteries were entirely independent of the parenchymal injury since similar changes are noted in the pancreas, heart and kidneys. Material found in the follicular arteries and the larger arteries of the trabeculae can hardly be considered as derived from the necrotic parenchyma, since the two substances are morphologically different. The substance filling these arteries appeared to be derived from the walls of the vessels except in a few arteries of the trabeculae which contained thrombi. Although a toxic condition is associated in cases of flecked spleen, it is doubtful that this factor plays a direct part in the production of the infarct-like areas of necrosis of the spleen, as necrosis of this type is not seen in pronounced uremia of essential hypertension without marked lesions of the small splenic vessels.

It is difficult to account for the rarity of flecked spleen. Whereas it has been shown that the condition occurs in by far the majority of cases in association with essential hypertension terminating in uremia, the association of the two conditions is rare. Klemperer and Otani [10] found but one instance in eighteen cases of malignant nephrosclerosis. Bell and Clawson [17] found no example in thirty-six cases of essential hypertension associated with uremia. On the other hand, the vessels of the spleen frequently show changes in generalized atherosclerosis and hypertension (Fishberg,[26] Spier [24] and others). It was shown by Herxheimer,[27] in a study of the spleens of 1,140 normal persons, that hyaline degeneration of the small vessels occurs as early as the age of 10 years and

25. Heuck, W.: München. med. Wchnschr. **67**:535, 1920.
26. Fishberg, A. M.: Arch. Int. Med. **35**:650, 1925.
27. Herxheimer, G.: Berl. klin. Wchnschr. **54**:82, 1917.

increases during life. Obviously marked narrowing of the small arteries under normal conditions and in most cases of arteriolosclerosis does not produce necrosis of the parenchyma. The rich vascular supply of the pulp evidently compensates for the marked restriction in size of the peripheral arterial circulation in the majority of cases. It is only in rare instances in which there is extensive occlusion of the small arteries that the lesions of flecked spleen occur.

SUMMARY

Flecked spleen of Feitis is an extremely rare condition characterized by nonembolic multiple areas of anemic necrosis.

The necrosis is due to occlusion of the splenic arteries of small and medium size. On the basis of the nature of the vascular lesion, three types of flecked spleen are recognized: (1) arteriosclerotic, (2) arteritic and (3) thrombotic. The arteriosclerotic form is the most common, comprising all but three of the twenty-one cases of flecked spleen described in the literature.

The arteriosclerotic form of flecked spleen is associated with renal lesions of hypertension, which in most cases produce death from uremia. The thrombotic form, described in a report of a case of eclampsia, is associated with multiple necroses of the kidney. The arteritic type is described in association with two cases of glomerulonephritis.

Flecked spleen should be differentiated from multiple necroses of the malpighian corpuscles associated with acute infectious diseases, as the pathologic changes and pathogenesis in the two conditions are dissimilar.

A case of flecked spleen is described in which the anatomic and histologic changes were similar to those reported by Feitis. The kidneys show the lesions of an advanced stage of arteriosclerosis accompanied by arteriolonecrosis.

STRUCTURAL CHANGES IN THE GRANULAR LAYER OF THE CEREBELLUM

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The purpose of this study was to determine if, among the various pathologic lesions of the cerebellum already described, there could be added another condition which has been recorded under the terminology of "conglutination of the granular layer," and if other pathologic changes of the same layer could be found.

Conglutination consists of a clumping of numerous cells of the granular layer which lose their individuality and form irregular and solid masses of elements undergoing a more or less advanced degeneration. Such pathologic changes, which have already been described by Ferraro and Morrison [1] in various experimental conditions, have been investigated in the course of this study in animals and in various human pathologic conditions.

For practical purposes the cortex of the cerebellum may be divided into: (1) the outer layer or molecular layer which contains few medullated fibers and few nerve cells; (2) the nuclear layer, better known as the granular layer; (3) the layer of Purkinje cells, formed by flask-shaped elements situated between these two other layers.

The granular layer is formed by nuclei of cells rather closely packed together, with here and there clear spaces between them, and forming what is known to some authors as islands or glomeruli of the cerebellum. Scattered throughout are larger cells known as Golgi cells. Hence the two chief cells of this layer are granular cells and Golgi cells.

The granular cells are karyochrome in type and are rather small, about 0.7 micron in diameter. Their nucleus is rather large and surrounded by a cytoplasmic ring which is fairly narrow. Each cell has from three to six fairly short dendrites which terminate close to the cell body in what may be called a limited arborization. Where these arborizations meet, there results an apparent empty space known as dendritic islands. The axons of the granular cells extend through the

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From the Department of Neuropathology of the New York State Psychiatric Institute and Hospital.

1. Ferraro, A., and Morrison, R.: Psychiat. Quart. **3**:506, 1928.

superficial, deep and intermediate levels of the molecular layer, from all of which positions they give rise to the typical T-shaped and at times Y-shaped branches. They are without myelin sheaths. The type of synaptic union between the axons of the granular cells and the dendrites of the Purkinje cells is the cruciform variety and thus brings about extensive Purkinje synaptic connections.

Three varieties of stellate cells of Golgi are recognized in the granular layer, the most important being the stellate corpuscles.

In the embryonal development of the cerebellum in man as well as in animals there is besides this granular layer the external granular layer which is to be found external to the molecular layer. The cells of this external molecular layer are known as the cells of Obersteiner. They gradually disappear, and in man two years after birth they are no longer present.

In animals, more particularly in cats, this external layer of granules which is pronounced immediately after birth gradually disappears, and in cats 6 weeks old the layer is practically absent.

Three kittens and two adult cats were examined for purposes of control, and while the new-born animals showed a considerable number of cells in the external granular layer, the animal 5 weeks old showed a marked decrease in the number of cells and width of the layer. The external granular layer in the new-born cat is apparently formed by cells running in two directions; in the outer layer the cells form rows which are perpendicular to the inner layer, the course of which is parallel to the external surface of the molecular layer (fig. 1).

Though even in normal conditions the cells of the internal granular layer have a tendency to form glomeruli as already mentioned (fig. 2), there is no evidence of any abnormal clumping, fusion or conglutination of the elements, comparable with the pathologic picture in "conglutination."

It must be mentioned, however, that another adult animal that was used for control disclosed a slight amount of conglutination, which fact led me to the belief that in this particular case a pathologic process of unknown nature must have been active in the animal and caused pathologic changes in the granular layer. That such must be the case is also indicated by the fact that in a large series of other animals, though they were in a pathologic condition, conglutination was entirely absent.

In order to establish if postmortem changes could determine the occurrence of conglutination in the granular cells of the cerebellum,

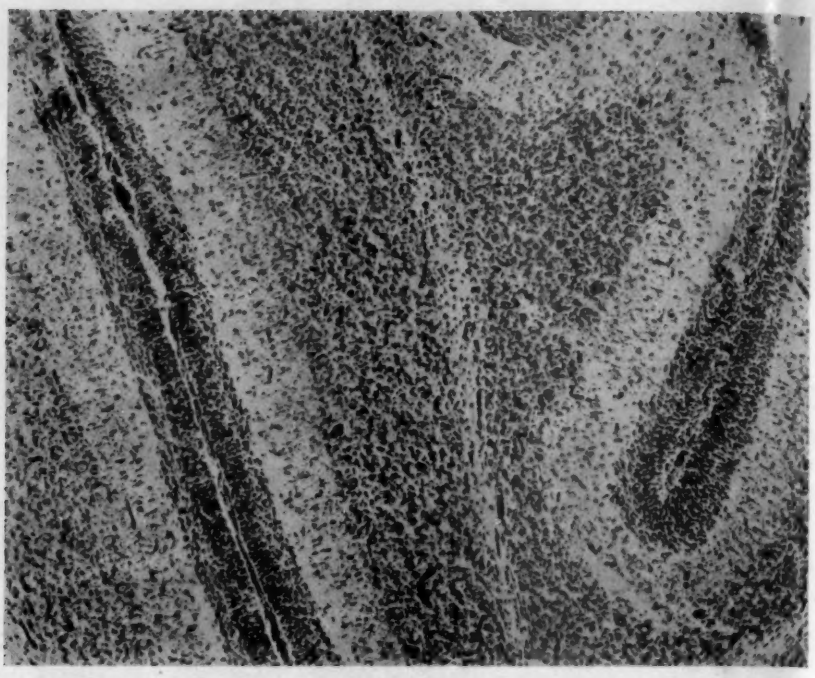

Fig. 1.—Presence of an external granular layer in a new-born cat. Note the existence of two rows of cells perpendicular to each other. Nissl stain.

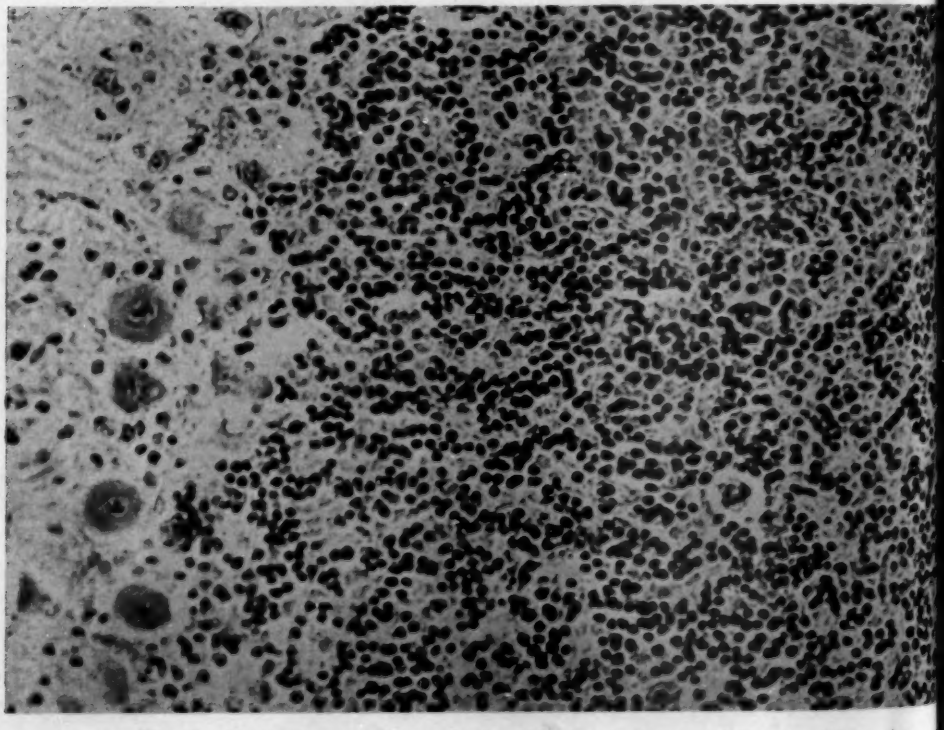

Fig. 2.—Normal appearance of granular layer in an adult cat. Note the tendency of formation of cerebellar glomeruli in which, however, each cell maintains its own individuality. Nissl stain.

partial removal of the cerebellum was done immediately after the death of a cat, twenty-four and thirty-six hours following death. The purpose was to see if the time between death and fixation would have any influence in establishing conglutination. It was found that none of the specimens showed any conglutination.

EXPERIMENTAL WORK

In investigating the reaction of the granular layer to various pathologic conditions, twelve cats were subjected to experimental lead poisoning (table 1). In the first group of animals lead carbonate was administered orally; in the second group lead was given intravenously

TABLE 1.—*Experimental Lead Poisoning*

Group	Cats	Total Weight Drugs, Gm.	Mode of Administration	Single Dosage	Days Before Death
1	1	57.0	Lead carbonate orally, daily	0.74 Gm.	78
1	2	44.0		0.71 Gm.	62
1	3	49.0		0.84 Gm.	58
2	13	9.0	Intravenously, 15 cc. of 1% solution lead acetate and orally as lead carbonate	1.5 cc.	33
2	12	17.0		1.5 Gm.	21
3	5	0.60	Acetate of lead, intravenously and daily	20 cc. of 1% sol.	3
3	6	0.40		10 cc.	4
3	7	0.22		2 cc.	11
4	8	0.15	Acetate of lead, 1% solution, intravenously	5 cc.	3
4	9	0.15		3 cc.	5
4	11	0.20		2 cc.	10
4	12	0.20		10 cc.	2

as lead acetate, and by mouth as lead carbonate; in the third group lead acetate exclusively was given intravenously. The animals in these groups were allowed to die from the effect of the poisoning, whereas in the next group, in which lead acetate was also used intravenously, the animals were killed after fixed periods of time in order to study the early stage of reaction.

As a result of the study of these twelve cats, I reached the conclusion that in the long-standing cases, particularly in the three animals of the first group, conglutination was present, but the main pathologic change was the rarefaction of the granular layer. As a matter of fact, the number of cells present in this layer was considerably less than normal. This disappearance of cells, as represented in figure 3, seems to be parallel with the disappearance of cells of the Purkinje layer which also suffer considerable loss from lead poisoning. In the cases of group 2 conglutination was present in the two animals, and a slight

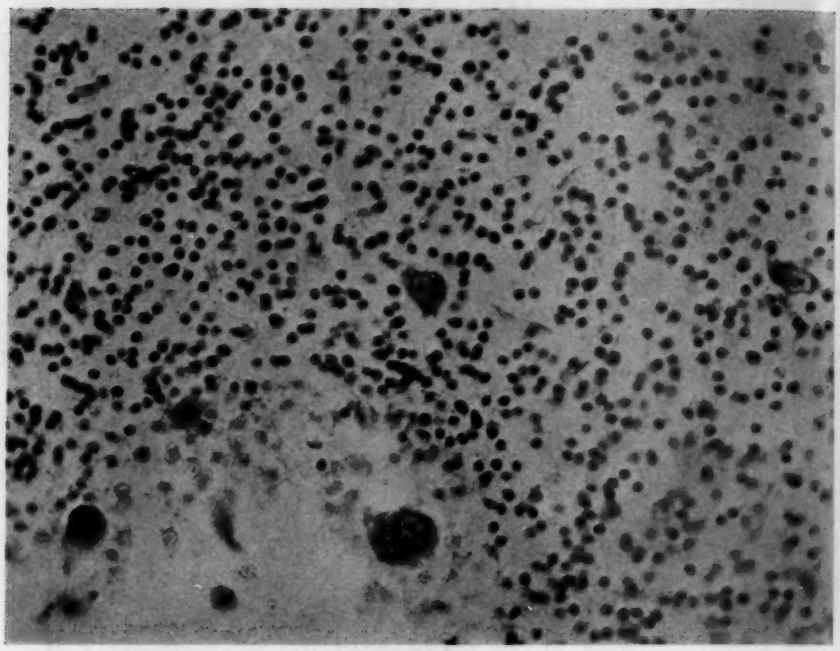

Fig. 3.—Rarefaction of the granular cells resulting in a widespread distribution of the remaining elements. Nissl stain.

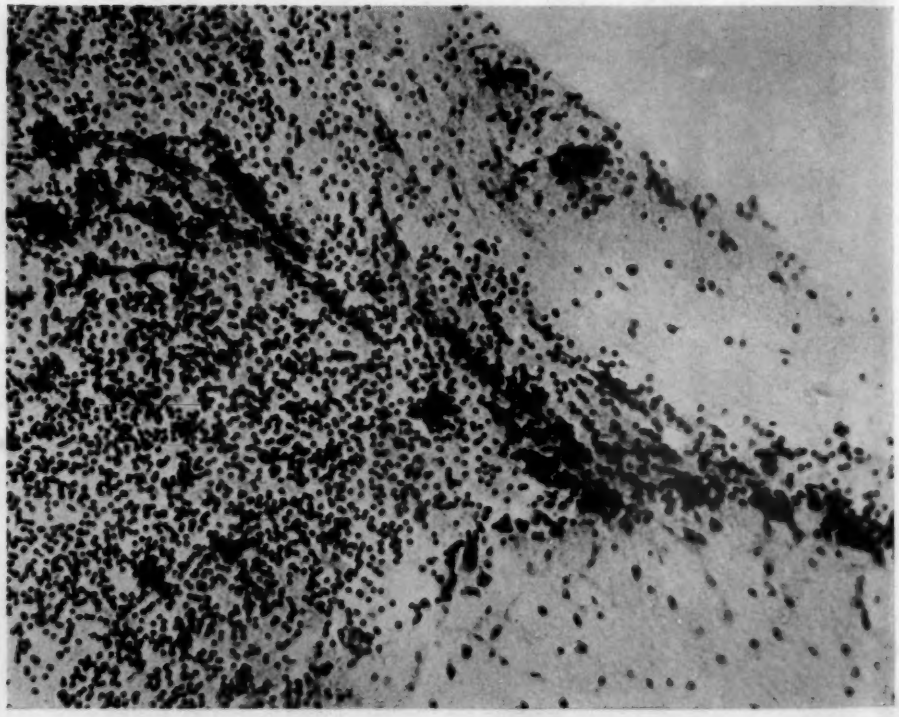

Fig. 4.—Marked conglutination of the granular cells in indole and histamine poisoning. Nissl stain.

rarefaction was also noticeable. In group 3, the third animal, cat 7, showed slight conglutination associated with a slight loss of granular cells. In the fourth group conglutination was evident, particularly in cat 8.

Altogether, it seems that the more acute the lesion and the larger the amount of lead the more conglutination is evident, whereas the longer the animal survives the more the destruction of granular cells

TABLE 2.—*Experiments with Indole, Histamine, Potassium Cyanide Poisoning*

Cats	Weight in Kg.	Total Amount Given	Mode of Administration	Single Dosage	Days Before Death
3	3.25	0.5 Gm. indole	Hypodermically in olive oil (3 injections of 100 mg. each and 73 injections of 150 mg. each)	0.25 Gm.	2
6	3.6	11.25 Gm. indole		.....	96
2	3	1 Gm. indole	Hypodermically in olive oil	0.5 Gm.	2
E	3.5	2.6 Gm. indole 0.7 Gm. histamine	Hypodermically in olive oil	100 mg. 25 mg.	41
D	3	1.2 Gm. indole 0.3 Gm. histamine	Hypodermically in olive oil	100 mg. 25 mg.	12
8	4.4	6.6 Gm. indole 2.6 Gm. histamine	Hypodermically in olive oil	100 mg. 40 mg.	92
C	3.2	13 Gm. histamine	Hypodermically	Increasing from 5 to 80 mg.	82
9	...	1.5 Gm. indole 10 mg. potassium cyanide	Hypodermically	150 mg. 0.5 mg. in increasing doses to 2.5 mg.	13
9	4.2	600 mg. indole 7 mg. potassium cyanide	Hypodermically	100 mg. 2.5 mg.	6
Dinky	3	516 mg. potassium cyanide	Hypodermically	2.3 mg. in increasing doses to 28 mg.	37

takes place, thus upholding the conception that the cells undergoing conglutination later degenerate and disappear, the process resulting in a scarcity of the granular element.

The next group consists of eleven cats poisoned with histamine, indole, potassium cyanide or a combination of any two of these drugs (table 2).

Among the cats poisoned with indole a certain amount of conglutination was found in the granular layers, particularly in cat 3. In the

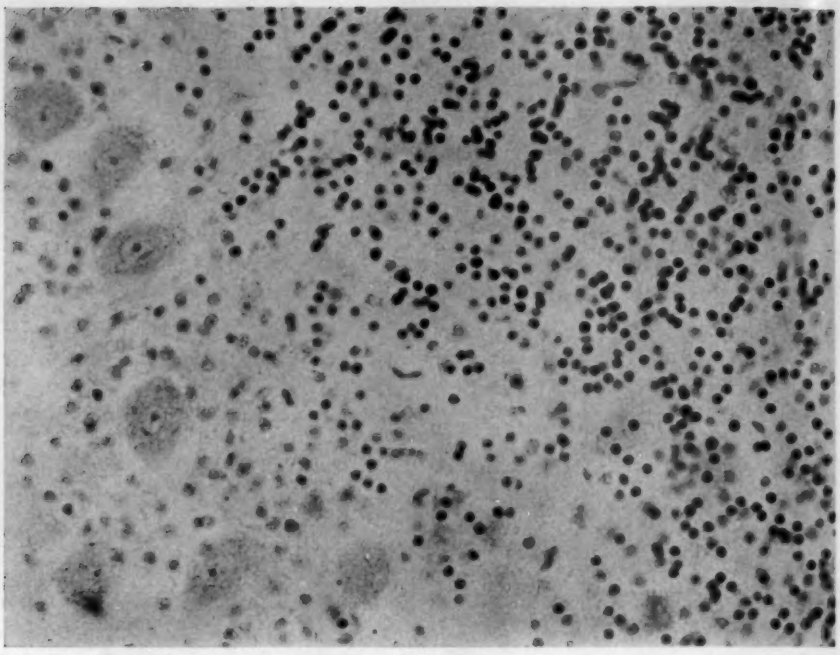

Fig. 5.—Rarefaction of the granular cells in a case of potassium cyanide poisoning. Nissl stain.

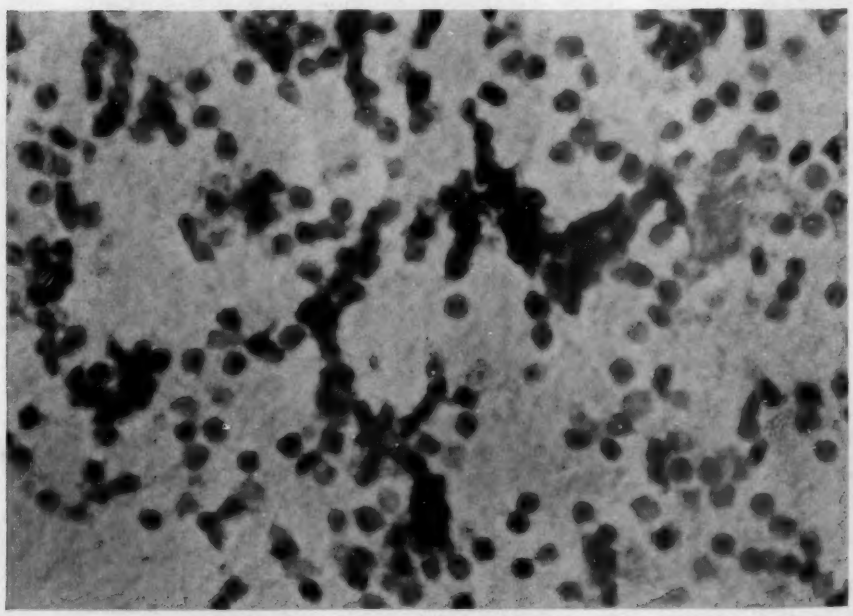

Fig. 6.—Conglutination of the granular layer in a case of illuminating gas poisoning. Nissl stain.

group poisoned with indole and histamine, the conglutination was much more pronounced, particularly in cat D (fig. 4). In cat C, which received 13 Gm. of histamine subcutaneously, there was an evident conglutination associated with loss of granular cells. In the group in which indole and potassium cyanide are used conglutination and disappearance of cells were found. In the cat, Dinky, which received 516 mg. of potassium cyanide, conglutination was not present in any noticeable amount, but there was considerable loss of cells in the granular layer (fig. 5).

Another experimental group included two cats, L and M, which died from provoked inanition. Cat L, which died on the forty-first day, was allowed to drink water during the experiment. This animal did not show conglutination, whereas cat M, which died on the fifty-second day of the experiment and which was not allowed to have any water, showed a certain amount of conglutination of the granular cells.

Rabbits were also studied under experimental conditions of repeated illuminating gas poisoning and of repeated intravenous injections of hypotonic solution.

Of the first group, five animals were examined after various periods of gassing through a glass chamber in which the animals were placed and into which two tubes carried illuminating gas and oxygen, respectively. In these five animals there were evident traces of conglutination. In the most advanced cases there was also a destruction of granular cells. Figure 6 illustrates conglutination in an animal which had been gassed eight times in thirty-five days. It can be seen that while some of the elements are fused together, others are in a more or less advanced state of degeneration.

Seven rabbits were treated with intravenous injections of hypotonic solution. They received various and repeated amounts of the hypotonic solution, from 35 cc. of distilled water to 950 cc. The number of injections varied from one in the rabbit which received 35 cc. to twelve in the rabbit which received 950 cc. The injections were given under sterile precautions in the auricular vein at intervals of twenty-four hours. The animals were killed after the last injection. In this series no conglutination was found. Conversely, there was a tendency of the cells of the granular layer to swell up and acquire a more marked individuality than normally. Because of the hydropic condition of the single elements, the cells appear to be stained less deeply than normally. Small vacuoles were noticeable in some of the cells (fig. 7).

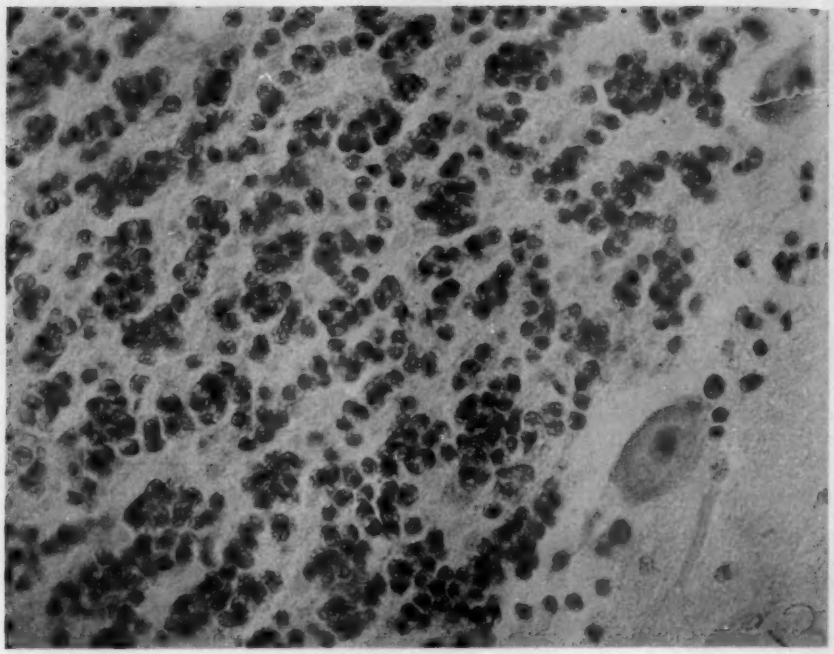

Fig. 7.—Swelling and vacuolation of the granular cells of the cerebellum following intravenous injection of hypotonic solution in rabbits. Hematoxylin and eosin stain.

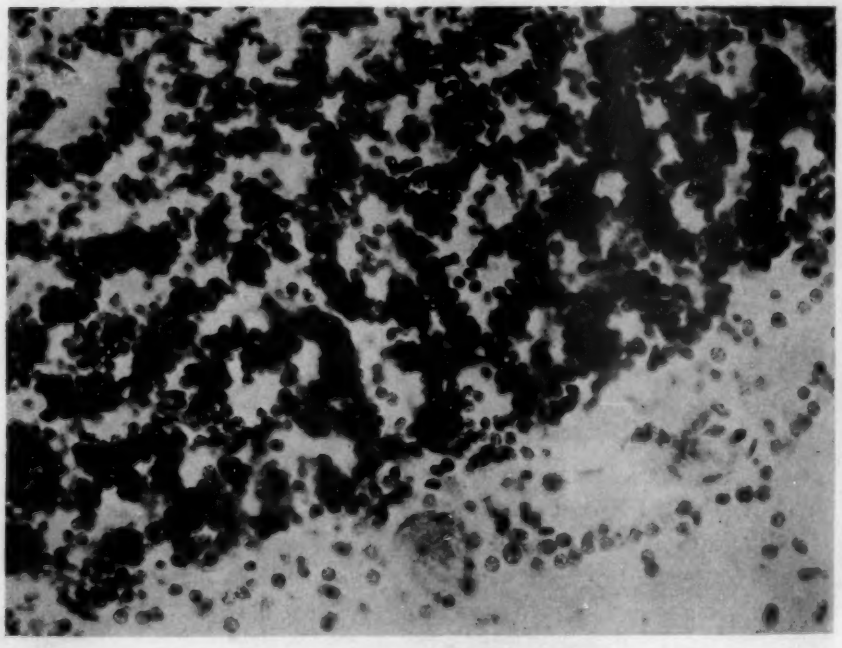

Fig. 8.—Conglutination in a case of dementia paralytica. Nissl stain.

HUMAN MATERIAL

Normal Control.—In order to study the distribution of these granular cells in normal persons, three cases of sudden accidental death were studied. Conglutination was not found.

Pathologic Material.—In the following cases the histologic changes in the granular layer were studied: dementia praecox, four cases; dementia paralytica, five; cerebral syphilis, four; Huntington's chorea, three; Schilder's disease, two; various types of acute meningitis, five; electrocution, two; epidemic encephalitis, two.

In the cases of dementia praecox there was no conglutination except that in one case there were indications of conglutination in a few areas.

In dementia paralytica the results were not constant; in some instances conglutination was absent, and in other instances present and even marked. Figure 8 shows definite conglutination, though some of the cells that come together still have preserved their individuality.

In cerebral syphilis no conglutination was present as a rule but rather a rarefaction of the cellular elements.

In epidemic encephalitis conglutination was present in one of the two cases but not uniformly or in severe degree.

In the two cases of Huntington's chorea loss of granular cells was found but no conglutination.

In the two cases of Schilder's disease there was no conglutination, but a definite loss of granular cells in association with a considerable amount of gliosis which was evident in the intercellular spaces, thus making the loss of cells more discernible (fig. 9).

In the group of septic meningitis all the cases showed more or less well marked conglutination.

In the two cases of death from electrocution no conglutination was found, but conversely a certain amount of swelling in the individual cells which appear more distinct though poorly stained. The condition resembles somewhat the condition described following the injection of hypotonic solution in rabbits (fig. 10).

SUMMARY

In addition to pathologic changes of the other layers of the cerebellum, a particular type of structural change has been found to be quite common in the granular layer of the cerebellum.

The granular cells of the cerebellum may collect or fuse into smaller and larger clumps in which the individual cells lose their outline and

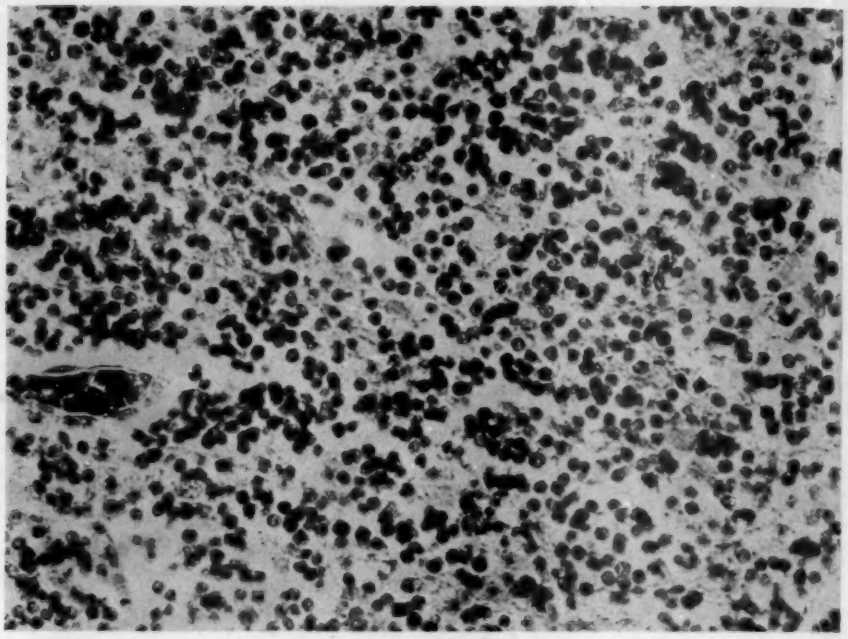

Fig. 9.—Rarefaction of the granular cells and intercellular gliosis in a case of Schilder's disease (diffuse sclerosis). Hematoxylin and eosin stain.

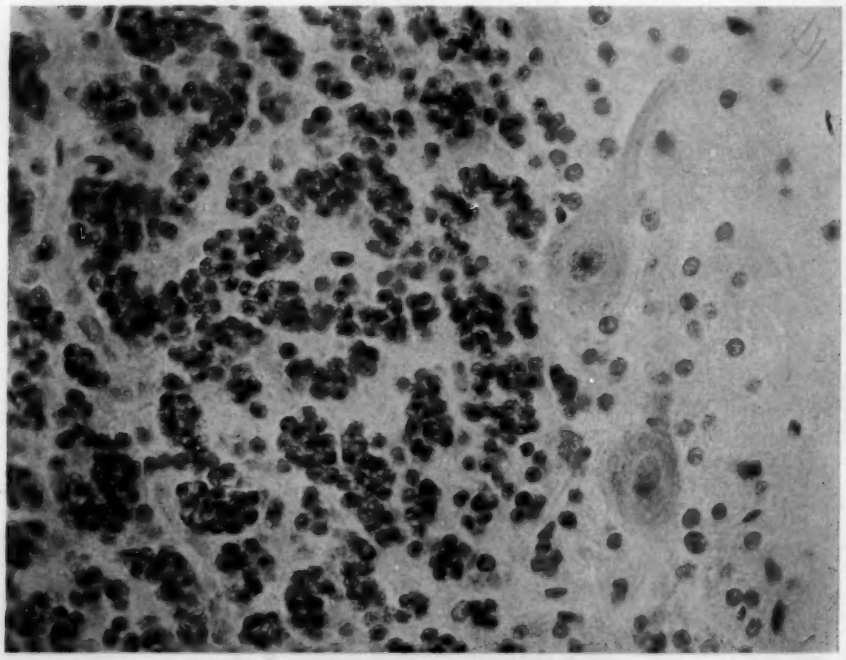

Fig. 10.—Swelling of the cells of the granular layer in a case of electrocution. Hematoxylin and eosin stain.

gradually undergo degeneration. Such a condition has been termed by Ferraro and Morrison conglutination of the granular cells.

Conglutination of the granular cells is not a specific process, but occurs under a variety of pathologic conditions. It is found in acute as well as in chronic processes, but seems to be more pronounced in toxic and infectious conditions.

Besides the process of conglutination other changes are described:

1. Rarefaction of the granular cells, a condition which might be the result of a previous conglutination. The rarefaction of the granular cells can, however, be independent of conglutination.

2. A process of acute swelling of the granular cells in which the single elements appear swollen, at times vacuolated, with a tendency to become more distinct and, apparently because of the hydropic condition, to stain poorly. This dropsical condition has been found following the injection of hypotonic solution in rabbits and in two cases of electrocution.

3. Rarefaction of the granular cells associated with interstitial gliosis was found in two cases of Schilder's disease.

General Review

SIGNIFICANCE OF SULPHYDRYL AS A GROWTH FACTOR

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Since the demonstration of glutathione in living material by Hopkins in 1921 numerous workers have studied the rôle which glutathione and sulphydryl compounds in general play in the activities of cells. Among the claims made in this respect, those connecting sulphydryl (—SH) with the multiplication or with the destruction of cells are especially interesting from the standpoint of research on cancer. The evidence brought forward by the various investigators is, however, often inconsistent with well established facts in regard to conditions controlling cell proliferation, and the conclusions drawn by them concerning the significance of sulphydryl for this process are contradictory. A review and a critical analysis of the experimental work on this subject seem, therefore, to be indicated. It is hoped that a study of the evidence presented and a testing of the validity of the conclusions reached may clarify the situation.

SULPHYDRYL COMPOUNDS AS ESSENTIAL NUTRITIVE SUBSTANCES

It has been known for some time that cystine, the oxidized form (S = S) of the sulphydryl-containing amino-acid cysteine belongs to that restricted group of amino-acids which are indispensable for normal growth and development of the animal organism and for synthesis of its proteins. Animals kept on a diet deficient in cystine show lowered vitality, greatly retarded growth and defective formation of hair as well as a drop in the glutathione content of the organism (Lightbody and Lewis; Mitchell and Hamilton; Marenzi and Laclau). Gudernatsch and Hoffman showed that the growth of tadpoles kept in a medium containing amino-acids as the sole supply of nitrogen is stimulated by cystine.

Baker demonstrated that the growth of sarcomatous fibroblasts explanted into an artificial, nutritionally deficient medium was markedly stimulated by the addition to the medium of glutathione in combination with liver ash and hemoglobin. This action on cell growth became apparent, however, only when the cells were grown in a medium deficient

in the proper food material. If fibroblasts were explanted in a medium composed of equal parts of chicken plasma and embryo extract diluted with Tyrode's solution in the proportion 1:25, a moderate growth resulted, which could be appreciably increased if glutathione was added to the medium in amounts equivalent to the amounts present in embryo extract diluted with Tyrode's solution in the proportion 1:4 (Hueper and Russell).

The great prominence which sulphydryl compounds (cysteine, reduced glutathione, thioneine and possibly also thiolactic acid and thioglycollic acid, besides the thioproteins) have obtained in recent years is, however, due not to their nutritive value but to their possible importance as cellular catalysts which control and regulate, directly or indirectly, vital processes of the cells, including especially cell multiplication and cell destruction by proteolysis.

SULPHYDRYL AND NORMAL GROWTH

Among the authors who have stated that the sulphydryl group is essential for cell multiplication and acts as a stimulus to this process, Hammett has made the most far-reaching claims, and his work may therefore serve as the basis of the present discussion. From the results of his numerous experiments with plant and animal material, working with minute amounts of sulphur compounds, he concluded that sulphydryl, as the substance occurring naturally in the cell, is the essential and universal stimulus to growth by increase in the number of cells, and that the reaction-product derivatives of sulphydryl are the natural inhibitors of this process, so that the stimulation by sulphydryl is normally limited by the inhibitory action of the suboxidized sulphur forms of sulphydryl (—SO; —SO_2; —SO_3) resulting from the normal oxidation of sulphydryl. Cell proliferation is therefore regulated by the intracellular equilibrium of —SH —SO_3, according to Hammett and Reimann. The countless other factors which apparently have an accelerating influence on mitosis exert it, according to Hammett, only through their effect on the sulphydryl groups rather than directly. He asserted, furthermore, that the acceleration and forcing of cell division by the sulphydryl stimulus in cells with a normal chromosomal constitution result secondarily and without direct relation to the action of sulphydryl in an enhancement of differentiation and organization of the cells, which may reach degrees beyond those ordinarily attained. An explanation of the mechanism of the action of sulphydryl in cell division was, however, not offered by Hammett.

In support of his contentions, Hammett pointed out that sulphydryl-containing substances are naturally concentrated in regions where growth by cell proliferation is actively taking place. This observation is correct

so far as it has been shown by various investigators (Lund; White, Baumann and Webster; Camp; Binet, Leon and Magrou) that sulphydryl-containing substances are accumulated in the young, actively growing parts of plants (root tips and apical ends) while they are diminished or absent in the mature parts. It has also been noted that the breaking of dormancy of potato tubers, gladiolus corms, peas, etc., is accompanied by an increase in reducing substances, especially in glutathione, in the tissues. The increase in the reducing power of the juice of the activated tubers and corms is, however, only one-fourth due to glutathione, the rest of the effect being caused by some unknown reducing substances, among which may possibly be hexuronic acid (ascorbinic acid) recently described by Svirbely and Szent-Györgyi as representing vitamin C in plants and having strong reducing qualities.

It may, furthermore, be mentioned that various sulphur compounds, such as thio-urea, sodium thiocyanate, thiosemicarbaside and thioglycollic acid, have been found to be especially effective in breaking dormancy. But there are numerous other agents, such as ethylene chlorhydrine, hydrogen dioxide, hydrogen, nitrogen, acetylene, light and darkness, by which dormant tubers can be activated (Guthrie; Firket and Comhaire). Guthrie stated that chemicals found effective in breaking dormancy are (1) those that produce an increase in the p_H and hence an increase in sulphydryl groups and (2) those that produce only small changes in the p_H and the reducing power of the juice, such as potassium sulphocyanate and thio-urea. However, according to Firket and Comhaire, no relation exists between the intensity of growth and the relative amount of glutathione in germinating peas, and the glutathione is not localized in any predominant manner in the regions of cell multiplication.

That there does not exist any definite rule in regard to sulphydryl concentration and cell multiplication is also evident from observations of Guthrie, Denny and Miller, who found that the treatment of non-dormant potato tubers with ethylene chlorhydrine resulted, not in an increase, but in a retardation, of the rate of growth in spite of a marked increase in the reducing power of the juice, which indicates a considerable elevation of the sulphydryl content of the treated tubers above the normal value.

Proliferating animal tissue also apparently contains considerable amounts of sulphydryl-containing substances, according to the findings of various investigators (Yaoi; Kamiya; Murray; Binet, Leon and Magrou; Voegtlin and his associates). Voegtlin and Thompson stated that the glutathione content of the body declines with age, dropping to about one third of its highest peak in embryonal life, and that this drop runs parallel with that of the growth rate. But though chicken embryo extract contains large amounts of glutathione paralleling those in the

tissues of the body (Yaoi), there is not a gradual decrease in sulphydryl content conforming with the decrease in the growth rate of the embryo and the increase in differentiation. The glutathione content rises from 0.05 mg. per hundred cubic centimeters on the fourth day of incubation to 0.107 mg. on the twelfth day, declining again to 0.058 mg. on the twentieth day.

The growth-promoting effect of embryo extract cannot well be attributed to its content of free sulphydryl-containing substances, or the arrest of unrestricted growth attributed to the accumulation of inhibitory products of the oxidation of sulphydryl in the medium, for Hueper and his co-workers showed that the complete destruction of sulphydryl and the resulting production of oxidation substances in embryo extract by ultraviolet irradiation do not result in a decrease of its proliferation-stimulating qualities. Moreover, the fact that powdered embryo extract (Borger and Zenker) remains potent for more than six months, during which any free sulphydryl is certainly oxidized by the oxygen of the air into substances of the —SO, —SO_2 and—SO_3 type (according to Hammett) does not support the assumption of the exclusive rôle of sulphydryl in cell division.

The mere fact that a certain substance is accumulated in proliferating tissue is, moreover, insufficient proof of its relation to cell multiplication. Other substances (copper and arginine, for instance) are present in increased amounts in tissues of this type.

The assumption of Hammett that the sulphydryl content of liver tissue and liver extract is the hematopoiesis-stimulating principle appears to be insecurely founded in view of the fact that the iron and copper present in these substances may also be responsible for the aforementioned action. While Fleming would like to connect the oxidized form of glutathione with the antianemic qualities of the liver extract, Koegel showed that glutathione and other sulphydryl-containing substances accelerate the decomposition of blood in vivo on account of the hemoglobin-destroying action of sulphydryl. The presence of an antagonism between sulphydryl and the formation of blood is furthermore suggested by the experiments of Gruhzit with synthetic reduced and oxidized sulphydryl-containing compounds, which when fed to animals produced severe hemolytic anemia. On the basis of these observations it does not seem justified to connect the anemia observed in advanced cases of cancer with a deficiency of sulphydryl in the bone marrow, since no proof of the existence of such a condition has been offered.

This assertion is not supported by the fact that in anemic conditions the glutathione content of the individual erythrocytes is increased (Gabbe; Woodward and Fry; Varela; Nuomarco and Munilla), while the absolute amount of glutathione of the blood is decreased. This

observation agrees well with the finding of a normal or a low normal glutathione content in cancerous blood (Chatain; Varela, Apolo and Vilar; Woodward and Fry; Binet and Arnaudet; Ulibarri). The suggestion of Ulibarri that the low normal values obtained in cancerous conditions are caused by an absorption of sulphydryl by the malignant tissue does not seem to be justified in the light of evidence to be given later.

The presence of increased amounts of copper in organs and tissues rich in glutathione is of special significance, because it has been maintained that copper catalyzes the oxidation of sulphydryl (Locke and Main; Eliiot; Harrison) and that heavy metals, such as copper, lead, gold and arsenicals, are detoxicated in the organism by sulphydryl compounds (Voegtlin; Keesex; Labes). This interrelation gains importance for the problem, as Voegtlin, Rapkine and Hammett have used various heavy metals in their experiments to prove the thesis that sulphydryl stimulates or even is essential to cell division. Rapkine, using sea-urchins' eggs, obtained an inhibition of mitosis by the addition of mercuric chloride to the culture medium. Voegtlin, adding minute amounts of copper to the saline medium containing glutathione in which amebas were suspended, also found a decrease in the number of mitoses. Lead was used by Hammett in his experiments on root tips and paramecia; small amounts of lead salts added to the culture medium always caused inhibition of cell division. Hammett noted, furthermore, that no glutathione could be extracted from the root tips after the treatment with lead salts. He mentioned that the lead did not interfere with the growth in cell size and that extranuclear deposition of lead occurred most markedly in the regions where the concentration of glutathione was the greatest.

The determination of the lead content of the organs of animals that have received lead treatment does not support the view that lead is preferably deposited in the organs containing the highest amount of glutathione. Lead is found in largest amounts in bone, and then, in order, in muscle, kidney, liver and nerve tissue, while no appreciable quantities of lead are deposited in the skin (Aub, Fairhill, Minot and Reznikoff). If the organs mentioned were classified according to their glutathione content, they would appear almost in reverse order. It is known, furthermore, that the binding of the sulphydryl groups in the skin by arsenic (Voegtlin) results not in inhibition of growth, but rather in stimulation of cell growth, as hyperkeratoses and even carcinoma are often seen after prolonged arsenical medication (Hueper and Itami).

The rather discouraging results obtained with the lead treatment in that manifestation of growth *par excellence*, the cancer, do not point to a special affinity of proliferating, sulphydryl-containing tissues for

lead. As it has been maintained by Voegtlin that an increased glutathione content of the tissues protects against the toxic effects of heavy metals, one would suppose that not the proliferating cells with their higher sulphydryl content (Shearer; Chatton, Lwoff and Rapkine) but the resting cells would be most susceptible to the toxic action of heavy metals.

Heavy metals have, doubtless, affinities other than those to the sulphydryl compounds. Eichholtz listed as heavy metal complex-formers hexophosphoric acid, histidine, lecithin and other lipoids, pyrocatechine and guanidine derivatives and fragments of the hemoglobin molecule. Toxic action on cells by heavy metals can therefore be brought about not only by an elimination of the undoubtedly important sulphydryl groups but by interference with other substances essential for the proper functioning of the cellular processes, especially enzymatic activity, which might secondarily result in an inhibition of the reproductive process.

Hammett maintained that the inhibition of growth seen after the exposure of tissues to weak, nondestructive doses of radiant energy is due to the destruction of the sulphydryl compounds in the cells. The contention is based on his observation of inhibition of growth and retardation of differentiation in marine eggs irradiated for from five to ten minutes with gamma rays from a 15 mg. radium element, and on the decrease in color of the nitroprusside reaction in a watery solution of glutathione exposed for from six to twenty-four hours to the same dose of radium. Hammett was supported in this supposition by Coldwater, who irradiated planarians with 2,000 roentgens and saw simultaneously with the disappearance of the glutathione in the organisms a drop in their mitotic index from 83 to 65.75. In contrast to the minute amounts of radiant energy used by Hammett, Coldwater employed definitely destructive doses. He showed in subsequent experiments that the growth-inhibiting effect of the x-rays could not be neutralized by the addition of sulphydryl.

From the investigations of Hueper and his co-workers on embryo extract irradiated with large doses of beta and gamma rays, x-rays and ultraviolet rays, it appears to be unlikely that the rays used by Hammett and Coldwater exert an appreciable and direct effect on the glutathione content of the cells. Using embryo extract, a biologic material similar in many respects to the protoplasm of the cells and possessing eminent growth-stimulating qualities, Hueper and his co-workers irradiated this substance with from 15,600 to 31,200 roentgens and 255 and 323 millicurie hours. The results were as follows: X-rays have no destructive action, but possibly slight oxidation occurs; beta and gamma rays cause partial oxidation of the glutathione and slight destruction, that is, oxidation beyond the oxidized form (S — S). The same effects were produced

when glutathione in watery solution was exposed to the same types of radiant energy. Ultraviolet irradiation, on the other hand, caused marked oxidation and destruction of the glutathione. Glutathione in its reduced as well as in its oxidized form had entirely disappeared from the embryo extract in some instances after eight hours' exposure to ultraviolet rays.

These results prove rather definitely that x-rays and gamma rays used in therapeutic doses, especially in weak, nondestructive amounts, cannot have any appreciable direct oxidizing effect on the glutathione content of the cell, and that therefore the inhibition of growth observed after the application of these agents cannot be due to the direct elimination of the sulphydryl and the production of suboxidized sulphur in the cells. If the sulphydryl reaction becomes negative or decreases in intensity in the irradiated cells, this must be secondary and attributable to some primary changes in the protoplasm, for instance, in the enzymes (Hueper), caused by the rays.

Other observations also indicate that it is unlikely that radiant energy in small doses exerts a temporary inhibitory effect on cell growth. The carcinoma resulting from repeated prolonged exposures to small amounts of x-rays is well known. If the intracellular sulphydryl groups are so readily destroyed, as apparently Hammett and Coldwater assume, the existence of tumors which are refractory to roentgen rays and radium becomes unexplainable. Moreover, the occurrence of osteogenic sarcomas on the basis of chronic radium poisoning (Martland), a condition in which the cancer-producing tissues are constantly exposed to bombardment with beta and gamma rays, cannot be reconciled with the aforementioned claim. But even the application of ultraviolet rays, which, as has been shown by Hueper and his co-workers, Lieben and Molnar, and others, are able to produce oxidation of sulphydryl, does not result in inhibition of growth but can be the cause of malignant proliferation of cells, as it has been demonstrated by Putschar and Holtz, Herlitz, Jundell and Wahlgree, Abrikosoff and Weil, and Findley and Lawrence that prolonged exposure to ultraviolet rays can produce cutaneous cancer in man and in animals.

To add further support to the sulphydryl theory, Hammett and his co-workers performed experiments in which minute amounts of various sulphydryl compounds were mixed with the culture medium or injected into the organisms. An increase in the number of mitoses was noted in the growing root tips of Zea rays and in cultures of Paramecium when *p*-thiocresol or hydrogen sulphide was added to the mediums. The increase in proliferative activity was accompanied by a decrease in cell size. In the hermit crab acceleration of regenerative processes was observed after the addition of *p*-thiocresol to the sea

water in which the eggs were kept. Similar investigations in regard to cell proliferation were made on other marine eggs. *P*-thiocresol and glutathione, respectively, were added in similar concentrations to the sea water, and not only an acceleration of cell multiplication but an enhancement of cell differentiation and organization resulted in the experimental animals. The intratumoral injection of small amounts of thiodextrose caused, according to these authors, a more rapid growth of the tumors in comparison with that seen in tumors which received only equivalent amounts of dextrose. The local application of a 5 per cent benzyl mercaptan ointment to the skin of mice for from four to six months caused on the larger part of the body a thickening of the epithelium through proliferation of the younger, incompletely differentiated cells with the development of a regular base line, spinous cells and keratin and a downward growth of epithelial strands into the corium. Even an increase in the number of hair follicles was noted. In the remaining areas of the body, the epithelial changes were less pronounced; there was thickening of the connective tissue with an increase in vascularization and in elastic tissue formation. An inflammatory reaction was not present, according to the statements of Hammett and Reimann. The two authors reported also a hastening of the epithelization of cutaneous ulcers and a thickening of the epithelium of freshly healed wounds after application of a *p*-thiocresol ointment.

Some of the experiments mentioned have been repeated by other investigators, with negative results. Gaunt, using the eggs of two types of fresh water snails, added cysteine to the water and found that there was no acceleration of cell division as compared with eggs kept in plain water, while, following Hammett's example and advice, there was some increase in the number of mitoses in the cysteine series if equivalent amounts of *d l*-alanine were added to the water of the control series. The conclusion was therefore drawn that there was no evidence of a growth-stimulating action of cysteine and that the increase noted in the last mentioned experiment was spurious, since cysteine in the concentrations used was less toxic than *d l*-alanine.

Similar experiments were performed by Morgulis and Green with Podarke obscura. These authors added *p*-thiocresol, thiophenol, thioglycollic acid and cystine to sea water in concentrations approximating those employed by Hammett. No growth-stimulating effect was observed if the sulphydryl-containing substances were used in concentrations of the "effective" range, according to Hammett, while cell degenerations occurred when concentrations above this range were used, a result which to a certain extent was parallel to that obtained by Sullivan on feeding excessive amounts of cysteine to animals. Morgulis and Green objected, moreover, to the method of calculation used by Ham-

mett in the evaluation of his results, which tends to exaggerate grossly the actual differences.

Attention may be called in this connection to a statement of Lewis, that thiophenol and thiocresol resist oxidation in the organism as all mercaptan groups directly attached to a benzene nucleus do, while sulphur linkages of the character of the mercaptan group, or those which can easily be hydrolyzed to form this group (thio-urea or cysteine), are easily oxidized. The sulphydryl group in *p*-thiocresol is therefore in the organism rather stable and consequently chemically inert. For this reason, it is probable that the sulphydryl group in glutathione and in *p*-thiocresol will have a different biologic effect.

It is also unlikely that the hastening of healing of wounds by the application of extracts from macerated tissue can be attributed to the effect of sulphydryl as noted by Hammett, who referred to the observations of Carnot and Terris on extracts of macerated skin. Hammett's claim is based on the statement of Bierich and Kalle that, in autolysis, a liberation of sulphydryl-containing substances occurs; these, according to him, act as growth stimulators. McJunkin repeated the experiments of Carnot and Terris and found that macerated skin apparently accelerated the healing of cutaneous wounds, but that, on the other hand, the application of extracts of liver, which, as is well known, contains large amounts of glutathione, did not favor healing, but rather inhibited it. The observations made during experiments in vivo have been substantiated by experiments in vitro. Fischer mentioned that liver extract is the only extract which definitely inhibits cell proliferation. This finding was substantiated in the experiments of Hueper and his co-workers with normal and malignant tissues in vitro. Moreover, observations on tissue cultures do not support the assumption that the liberation of sulphydryl in cell degeneration stimulates proliferation because partial necrosis in tissue cultures inhibits growth (Fischer).

In reference to Hammett's experiments on marine organisms with sea water as the medium, it may be pointed out that some of the marine organisms contain, according to Blanchetière and Melon, not inconsiderable amounts of glutathione (from 24 to 174 mg. per hundred grams of tissue). In view of these relatively high amounts of glutathione in the adult animals and the probability that they are even greater in the eggs and embryos, it seems rather doubtful that the minute amounts of sulphydryl-containing substances added to the sea water should exert any appreciable biologic effect on their growth and development. As additional complicating factors the active iron and other heavy metals, such as copper, gold and manganese, dissolved in the seawater and the rather alkaline reaction (p_H 8 to 8.2) of the medium must also be given consideration. Both of these factors tend to favor

the rapid oxidation of any sulphydryl-containing substances added to the water (Harvey). It seems, therefore, to be rather improbable that the sulphydryl that was added reached the experimental animals in an unchanged condition.

Concerning the use of hydrogen sulphide as a substance containing sulphydryl and therefore stimulating mitosis (Hammett; Sharpe), Sun did not observe such an effect in sea-urchins' eggs. It cannot be assumed as certain that hydrogen sulphide and glutathione exert the same effect on the cell, as there is apparently a difference between the action of hydrogen sulphide and that of reduced glutathione on the respiratory mechanism (Dixon; Bumm and Appel). Hydrogen sulphide is, moreover, an exquisite cell poison, comparable in this respect with cyanogen (Moncorps).

The interpretation of the epithelial changes produced in the skin of mice painted with benzyl mercaptan as evidence of phylogenetic progression caused by sulphydryl seems to be rather far-fetched in view of the fact that similar formations can be produced in the mouse by other means (tar, 1:2:5:6 dibenzanthracene) and are common among the pathologic changes of human mucous membranes (leukoplakias). The pictures published with the respective papers do not support, moreover, the contention that the epithelial proliferations occur in the absence of an inflammatory reaction, because several pictures show a moderate but definite small round cell infiltration of the corium. The epithelial changes may, therefore, more likely be due to a low grade chronic inflammation. Considering also the facts that sulphydryl compounds are apparently used for the synthesis of keratin (Guroud and Bulliard), and that this process tends to be initiated in surface epithelial cells when through increase in the number of cell layers a gradual removal of the upper layers from the base of food supply occurs and thereby an interference with nutrition takes place (Mekie), the rôle which sulphydryl plays in phylogenesis does not appear to be as definitely established as Hammett asserts. The toxic nature of the sulphur compounds used in these experiments is well demonstrated by the occurrence of severe cutaneous reactions with formation of blisters in some instances in which 20 per cent thiocresol ointment was used (Reimann).

Moreover, the work of Voegtlin and his co-workers cannot be regarded as proof of the promotion of cell division by sulphydryl. Using amebas as test objects and reduced and oxidized glutathione in a buffered saline solution as the sulphydryl-containing medium, Voegtlin observed an increase in the number of mitoses in the experimental series in comparison with the control series which were kept either in the plain buffered saline solution or in a saline solution to which equivalent amounts of several amino-acids that do not contain sulphydryl were

added. It was noted that the addition of sulphydryl to the medium hastened the digestion of the material in the food vacuoles. The stimulation of cell division depended on the size of the cells. The small cells appeared to be refractory to stimulation with sulphydryl, indicating that the effect was a function of cell volume. Considering cell volume as a function of physiologic maturity or "differentiation" of the cell, the effect of glutathione depends, according to Voegtlin, on this factor. These observations and conclusions stand partly in direct contrast to those of Hammett, who connected the susceptibility to the sulphydryl-stimulus with the immature, small cells.

Certain objections can be raised against the experiments described. Among the amino-acids added in equivalent amounts to the control medium was alanine, which was also used by Hammett and Gaunt in their controls. As already mentioned in connection with Gaunt's work, alanine proved to be cell-toxic. That a similar action was exerted in Voegtlin's experiments is apparent from the survival rates of amebas kept in three different mediums (with glutathione, about 70 per cent; with plain saline solution, 60 per cent, and with saline solution plus alanine, 55 per cent). The amebas in the alanine-containing medium showed the lowest survival rate. It is obvious that such a toxic effect must have a definite influence on the rate of cellular division. No consideration, moreover, has been given to the possibility that glutathione might have served as an activator of proteolytic enzymes engaged in the degradation of the protein material contained in the dead amebas, thereby supplying the living organisms with certain quantities of food substances and in this way supporting their survival and proliferation. That such a process may have been active seems to be indicated from the observation recorded that the rate of digestion of the material in the food vacuoles of the amebas in the glutathione medium was accelerated.

In the selection of amino-acids for this type of experimentation, consideration must be given to the fact that the various amino-acids have different effects on the maintenance, growth and differentiation of the organisms used (Gudernatsch and Hoffman) or reliable and conclusive results will not be obtained. On account of the aforementioned conditions, Voegtlin's observations remain of doubtful value so far as the stimulating action of sulphydryl compounds on cell division is concerned.

The amount of intracellular sulphydryl evidently depends to a certain extent on the availability of oxygen, being increased whenever there is an insufficiency of oxygen. This deficiency of oxygen may be absolute or relative. When an absolute deficiency prevails a condition more or less incompatible with life exists and degenerative changes result. Owing to the decreased respiratory activity of the cell, an emergency and

auxiliary fermentative metabolism is resorted to by the cell for the production of the energy needed for the continuation of the vital processes. The lactic acid thus generated shifts the reaction of the cell toward the acid side, thereby favoring the stability and the production of the reduced form of sulphydryl in the cell. This type of intracellular increase in sulphydryl may be designated as the degenerative form.

On the other hand, excessively increased oxidative processes in the cell which demand an oxygen supply surpassing that which can be met by the normal resources of the tissue may result in a temporary and relative deficiency of oxygen and thereby cause an increase in cellular sulphydryl. This hyperoxidative type of intracellular increase in sulphydryl is apparently present in hyperthyroidism (Handovsky) and in organs with active cellular proliferation. It is obvious from these considerations that the presence of an increased amount of sulphydryl in a certain tissue may characterize two biologically different cellular states.

The evidence presented by the investigators cited in the foregoing discussion on the growth-promoting qualities of sulphydryl-containing substances does not offer sufficient proof of the thesis that sulphydryl is the essential and universal stimulus for normal growth in plants and animals. It remains doubtful whether the biologic activity of sulphydryl compounds favors cell division under all circumstances, or at all, as there exists evidence, partly already given and partly to be discussed later, which indicates that they may possibly act also as growth inhibitors.

SULPHYDRYL AND CANCEROUS GROWTH

In conformity with the claims made concerning the significance of sulphydryl compounds in regard to normal cell growth, several authors have attempted to relate these substances to the development and the proliferative activity of malignant tumors.

Hirsch asserted in his glutathione theory of canceration, as reported by Delbet and Franicevic, that canceration occurs when the glutathione accumulates or is at least relatively increased in the tissue, thereby disturbing the normal balance between the glutathione in the tissue and that in the blood. He bases his contention on the following observations: The glutathione content is elevated in the tissues of young animals and lowered in the blood during the period of greatest growth; in adult animals, chronic irritation causes an increase of sulphydryl in tissue comparable to that present during growth and thus produces a carcinogenic condition in the tissues; tar and arsenic lower the amount of glutathione in the blood, creating in regard to tissue glutathione a similar condition, that is, a relative increase and consequently a change in the oxidation-reduction potential between the tissues and the blood, which,

according to Hirsch, determines cell growth; young tumors contain an increased amount of glutathione, while it is diminished in the blood, and finally acidosis increases the glutathione in the blood, thereby removing a condition favorable to the development of cancer and cell multiplication in general.

Chatain is another investigator who has maintained that glutathione is a factor favorable to cancerous growth; he pointed out that this substance is increased in malignant tissue, and that cancerous growth is stimulated by insulin owing to its labile sulphur group.

Extending his conception of the action of sulphydryl on normal cell proliferation to the causative mechanism of malignant growths, Hammett proposed the following theory of the origin of cancer, which has been adopted and elaborated by Reimann: The biologic basis of malignant tumors is the distortion of the sulphydryl equilibrium in the presence in the body of genetically determined lines of cells in which the heightened nuclear reactivity or hypersensitivity to stimulation to proliferation by sulphydryl characteristic of young, incompletely differentiated cells is retained without resulting secondarily in increased differentiation. As the diverse architecture of malignant growths is essentially a consequence of the diverse anatomic and physiologic environments in which the proliferation of cells takes place, and as the increase in mitotic activity is in general followed by a decrease in the size of the cells, the rate of tumor growth is directly related to the interpretation of malignancy in terms of sulphydryl calculated from cell size. Sarcomas and carcinomas represent different responses to stimulation with sulphydryl in persons of different constitutional (connective tissue or epithelial) types. The difference in hydrogen ion concentration, carbohydrate metabolism and proteolytic activity of the malignant cell in comparison with the normal cell are but sequelae of the heightened reproductivity of the malignant cell.

In support of this theory, Hammett referred to the statement of Voegtlin and Thompson that tumor tissue contains glutathione in amounts comparable with those present in the liver, the organ having one of the greatest quantities of glutathione present in the various tissues. This high concentration is interpreted as due to the fact that tumors are composed of proliferating cells. The high sensitivity of embryonic cells to the sulphydryl stimulus is claimed to account for the development of tumors from embryonic rests (Cohnheim). The increased reduction power of cancerous blood, reported by Roffo, was attributed by Hammett to the probable presence of an increased amount of sulphydryl in the blood resulting from an overproduction of this substance by the malignant tissue. In reference to Roffo and Corea's observation in regard to the existence of insulinoid substances in tumor tissue, it is pointed out that, according to the observations of Adlersberg and

Perutz, insulin, containing suboxidized sulphur, stimulates the healing of old ulcers of the leg—a growth-stimulating effect which Hammett, however, could not substantiate in experiments with plant roots and paramecia. The observation that the loss of activity of Rous' sarcoma filtrate can be delayed by the addition of cysteine or glutathione (Gye and Purdy; Muller) is taken as indication either that the active growth principle present in this filtrate is sulphydryl or that its effectiveness is in some way related to sulphydryl.

The increased consumption of oxygen by malignant tissue, as reported by Russel and Gye, is considered as evidence for the increased concentration of sulphydryl in cancerous tissue requiring a heightened demand for oxygen. Tar cancer is attributed to the presence and growth-stimulating action of mercaptans and sulphides in the tar, promoting the generative processes beyond the level of repair. The frequency of metastases to lymph nodes is assumedly due to the facts that these organs are foci of cell proliferation and that proliferating cells respond best to the sulphydryl stimulus, while the high incidence of metastases to the liver is ascribed to the high concentration of glutathione in this organ, which is also supposed to be responsible for the hematopoiesis-stimulating effect of liver extracts, a contention already dealt with. The anemia so often encountered in the advanced stages of malignant tumors is assigned to a decline of the bone marrow, the decline being due to an accumulation of sulphydryl in the tumor corresponding to a general decrease in the rest of the organs (Voegtlin).

It is furthermore asserted that the hydrogen sulphide produced in the intestines by bacterial action, especially in the presence of constipation, may act as an etiologic factor in the development of cancer in constitutionally inclined persons. The infrequency of malignant growth in persons with hyperthyroidism is explained by the fact that this condition increases the oxidative processes in the body, causing oxidation of the sulphydryl group, which is highly sensitive to oxidizing agents. The cancer caused by Spiroptera neoplastica in rats (Fibiger) is laid to the production and fertilization of eggs, resulting in an increased concentration of sulphydryl (Shearer) in the tissues adequate to stimulate an abnormal proliferation of cells in a ground prepared by the inflammatory process and constitutionally inclined to a pathologic response.

Saunders held that the changes in the hydrogen ion concentration and the oxidation-reduction potential occurring in chronically inflamed tissues enable the sulphydryl groups present in the tissues, such as cysteine and glutathione, to act as a stimulus for cell division and to contribute to the causation of malignant growth. Saunders pointed out that, according to Hammett, sulphydryl is stable at p_H 5.5 and stimulative to growth; at p_H 7.2 it is changed to a suboxidized state, and therefore

retardation of cell multiplication results, whereas at p_H 6 to 7, a range in which an equilibrium exists between the reduced and the suboxidized form of sulphydryl, no consistent response is registered. He expresses the belief that the lactic acid produced by streptococci isolated from inflammatory and neoplastic tissues reduces the p_H of the tissue to about from 4.2 to 4.8, which keeps the sulphydryl in the stimulating phase.

If the evidence cited in support of the various theories respecting the part played by glutathione in canceration is evaluated, it soon becomes obvious that some of the data either allow a different interpretation or are contradicted by findings of other authors.

The statement of Voegtlin and Thompson that the high glutathione content of malignant tumors is comparable to that of the liver, one of the organs richest in this substance, is incorrect if judged by the figures given by these authors. In no instance does the glutathione content of the tumor (carcinoma and sarcoma) even approach that present in the liver of the animal; usually it is far below it, often being only one half or one third of that of the liver, or less. Bierich and Kalle stated, for instance, that malignant tissue contains approximately the same amount as normal tissue, adding that the glutathione content of a tumor apparently depends on its cellularity. A similar opinion was expressed by Hieger and Kennaway. Binet, Leon and Magrou noted that a greater amount of glutathione is present in normal growing tissue than in cancerous tissue. Holmes as well as Heinlein reported abnormally small quantities of glutathione in malignant tumors. Yaoi and Nakahara also recorded the presence of negligible amounts of glutathione in Rous' tumors, making Hammett's assumption concerning the relation of sulphydryl to the active principle of this tumor rather unlikely, especially in view of the observation of Murphy, who found that the nitroprusside reaction is negative in purified Rous' filtrate.

Voegtlin and Thompson observed a decrease in the glutathione content of the organs with the progress of the neoplastic growth. This observation was in general substantiated by Medvedev, who stated that carcinomatous tissue has a low glutathione content, but it was not confirmed by Bierich and Kalle. It must, however, be mentioned that apparently there is a drop not only in the glutathione content of the normal tissue, but in that of the tumor, according to the figures of Voegtlin and Thompson and Medvedev. These observations throw an interesting light on the investigations of Saxl, Kimura, Kahn and Postmontier and of Moravek on the total sulphur content of the urine and blood in cancerous persons. It was found by these workers that the total sulphur is increased in the urine and blood and decreased in the tumor tissue. These findings and the fact that various carcinogenic agents, such as arsenic, aniline and tar, are detoxicated in the body by sulphur (sulphydryl, according to Voegtlin and others) have caused

Grumme and Medvedev to maintain that cancer is a disease based on a deficiency in sulphur.

The question in regard to the state in which glutathione is present in the tumor tissue is still controversial. While Voegtlin and Thompson asserted that the glutathione in the tumor occurs mainly in the oxidized form, Bierich and Kalle expressed the reverse opinion.

As the majority of the authors cannot establish any extraordinary abundance of glutathione in neoplastic tissue or any relation between the amount of sulphydryl and the malignancy of the tumor (Binet, Leon and Magrou), no conclusions of definite value in regard to the significance of sulphydryl in the genesis and development of malignant neoplasms can be drawn.

The theory that glutathione is concerned in metastasis (Hammett) does not take account of the fact that mechanical factors regulate to a marked extent the distribution and implantation of secondary growths in the lymph nodes and the liver. The frequency of metastases in the lung, an organ with a moderate glutathione content and an excellent oxygen supply, remains entirely unexplained by such a theory. Primary tumors in the liver are, moreover, relatively uncommon, and metastases in the spleen, a lymphoid organ, are rare.

The anticancerous action of hyperthyroidism, referred to by Hammett as due to the stimulation of the oxidative processes in the body and the resulting destruction of sulphydryl, can also not be attributed to this mechanism, as Handovsky found that the feeding of thyroid tissue causes an increase of the organic glutathione. Handovsky added that whenever that tissue has an insufficient supply of oxygen either on account of poisoning of the respiratory ferment or on account of increased oxidation, glutathione in the tissue is increased. It must, furthermore, be kept in mind that glutathione as a respiratory catalyst accounts for only a part of the tissue respiration (Mann), and that cancer cells obtain their main source of energy from glycolysis, a process which cannot be suppressed by an increase of oxygen pressure, as the interrelation between respiration and fermentation expressed in the Pasteur reaction for normal cell metabolism does not exist for malignant cells.

It seems to be doubtful, moreover, that the acid reaction present in inflammatory tissue acts as a growth stimulant through its effect on the equilibrium between reduced and oxidized sulphydryl, causing a shift toward the reduced sulphydryl side. It is rather well established that normal as well as malignant cell proliferation is inhibited at an acid hydrogen-ion concentration (p_H 5.5), which is regarded by Hammett as the optimum for the stimulating effect of sulphydryl, and that, on the contrary, the growth optimum is found in the alkaline range at about

p_H 7.4 to 8 (Fischer; Balint and Weiss; Marton and Magassy, and many others), where sulphydryl is considerably less stable.

Demuth remarked that the growth of tumor cells proceeds less rapidly with an increase in the amount of lactic acid produced, and Reiss pointed out that the depression of the p_H of the environmental medium of malignant cells by the accumulation of lactic acid, either as the result of an excessive production of this substance or as the result of interference with its removal, may work as an inhibitory mechanism of self-regulation of tumor growth.

Considering the natural tendency of tissues to reduce glutathione (Dixon; Schiff and Fukuyama) and the fact that reduced glutathione becomes more stable and therefore inert (Mann), with an acid reaction (Joyet-Lavergne), and knowing that cell mitosis is a process requiring large amounts of energy (Needham) which are probably derived from oxidative processes and not from reducing ones, as Rapkine implied, one cannot readily conceive how a sulphydryl group of great stability, such as that present in acid tissue, could be responsible for the induction of mitosis. On the other hand, the great lability of the equilibrium between reduced and oxidized glutathione (SH—SS) in a biologic medium of alkaline reaction in which the reducing quality of the tissue is counteracted by the oxidizing tendency of the hydrogen ion concentration indicates that an SH—SS constellation of great reactivity should exist which might well take care of or participate in the production of the energy needed in mitosis and protein synthesis without which continuous cell proliferation is not possible. Hopkins attested to the higher reactivity of sulphydryl in an alkaline medium than in an acid one when he observed that oxidized glutathione is not an autoxidator in an acid medium, while it is in an alkaline one, where it is constantly reduced by the hydrogen donators in the presence of dehydrogenases of the tissue, as the autoxidation optimum of glutathione is found at p_H 7.4 (Dixon and Tunnicliffe). On the other hand, Hopkins demonstrated that on the acid side of p_H 7.4, the protein sulphydryl is oxidized, and the total amounts to ten times the equivalent of the sulphydryl present, while at p_H 7.4 to 7.6, the oxygen uptake amounts to only sufficient to oxidize sulphydryl.

The optimum hydrogen-ion concentration for growth is, moreover, closely related to the optimum hydrogen-ion concentration for glycolysis, which is found at p_H 7.58; glycolysis is almost lacking at p_H 5.8, according to Reding, Warburg and others. The restraining effect of an acid reaction on malignant growth, in spite of an apparently favorable concentration of sulphydryl, is therefore readily explained by the resulting inhibition of glycolysis, the main source of energy of the cells (Warburg, Posener and Negelein). The proper functioning of this important metabolic mechanism depends apparently to some extent on the alkalinity

of the medium. Sugar and sulphydryl compounds, being ubiquitous systems (Kuehnau), are evidently intimately interrelated in their biologic activity, as a high glutathione content is found in organs and regions which are centers of sugar metabolism (liver, suprarenal glands) (Kuehnau), a finding confirmed by Joyet-Lavergne. Niethammer observed, moreover, that germination of seeds does not occur and cannot be forced in the absence of sugar.

The direct dependence of the sulphydryl concentration on the intensity of the sugar oxidation is also shown by the fact that under certain conditions (dextrose oxidation) the liver can rapidly form large amounts of glutathione, from unknown sources, as long as the hepatic function is intact, while the sulphydryl fraction drops and becomes zero when this process is arrested.

The existing interrelation between the hydrogen ion concentration of the medium and the biologic activity of the sulphydryl system in malignant growth becomes significant in view of the considerable evidence which has been collected on the tendency of cancerous blood to be alkaline. Klobliha noted that proliferating cells have a somewhat less alkaline cytoplasm than normal cells, but that the cytoplasm of malignant cells, even if it is not basic by its own resources, can become alkaline by the action of the alkaline blood. Recent investigations with cultures of malignant cells kept under aerobic conditions have, moreover, shown that the supernatant fluid and the plasma-embryo extract medium become increasingly alkaline instead of increasingly acid as in anaerobic cultures (Hueper and Russell). As the aerobic conditions in the alkaline cultures correspond more closely to those present in the peripheral parts of malignant tumors, where the actively proliferating cells are in direct contact with the vascular system of the invaded normal tissues and therefore obtain an approximately normal supply of oxygen, these results may throw a new light on the vital activities of malignant cells in vivo and on the factors regulating them.

It is apparent from these data that the conditions existing in tumor tissue are not absolutely favorable to the stability of reduced cellular glutathione, but rather tend to make it labile and susceptible to oxidative agents. A growth-stimulating effect of sulphydryl-containing substances injected in minute amounts into tumors, as maintained by Hammett, is therefore scarcely probable and has not been confirmed by Gilroy.

The results of the great majority of investigators contradict the contention of Chatain and Hammett that insulin stimulates tumor growth (von Witzleben; Stuehlern; Piccaluga and Gioffari; Muenzer and Rupp, and others). It is, a priori, unlikely that a substance which decreases the dextrose content of the blood from which the tumor cells obtain their supply of this substance would act stimulatively on cell prolifera-

tion. Insulin and sulphydryl are, moreover, antagonists, as insulin is inactivated by cysteine (duVigneaud).

In regard to Hammett's assumption that the carcinogenic action of tar is due to its content of mercaptans and sulphides, reference may be made to the work of Burrows, Hieger and Kennaway, and Cook on the carcinogenic effect of synthetic benzanthracenes which they developed from their study of the purification products of tar, and which they relate to the carcinogenic quality of this substance. As these compounds do not contain any sulphydryl groups, this claim of Hammett seems to be rather insufficiently founded.

From the available evidence, as presented in the foregoing discussion, it can be concluded that the various theories as to the etiologic relation of glutathione and sulphydryl to canceration are not properly supported by definite facts. The great mass of observations and findings rather disproves them than sustains them. If one grants sulphydryl substances a contributory part in the development of malignant growth, it can be at best only a secondary rôle, remaining in the framework of their normal function.

ACTIVATION OF CELL DESTRUCTION BY SULPHYDRYL IN CANCER

The theoretical as well as practical weakness of the theories concerning sulphydryl and malignant growth is furthermore emphasized by the conceptions which are held by Waldschmidt-Leitz and Voegtlin in regard to the interrelations existing between the proteolytic processes and the activation of cathepsin by sulphydryl in malignant tumors.

On the basis of the observations of Grassmann that only reduced glutathione is an activator of proteolysis by cathepsin, Waldschmidt-Leitz proposed the theory that a connection exists between the oxidative and the hydrolytic processes in cancerous tissue. He contended that while in the normal cell, on account of the ample oxygen supply, the SH—SS equilibrium is shifted toward the oxidized form of glutathione, in the malignant tissue the existing oxygen deficiency, the production of lactic acid and the resulting acid reaction favor the stability of the reduced form of glutathione, resulting in optimal conditions for the activation of the intracellular protease, cathepsin, by sulphydryl. Waldschmidt-Leitz maintained that this constellation is responsible for the increased cellular proteolysis in malignant tumors, which is still more enhanced by the fact that the activator of cathepsin is considerably increased with tissue decay. In support of his theory, Waldschmidt-Leitz stated that the glutathione content of mature or old tumor tissue is higher than that of young tumor tissue. He referred also to the work of Mothes, who found that the activator of protein hydrolysis in plants is a sulphydryl-containing substance, while that of protein synthesis is

one of the character of oxidized glutathione (GSSG). The direction of protein metabolism in the plant depends, according to this author, on the oxygen potential. If oxygen is present in insufficient amounts, hydrolysis is activated; if it exists in excess, synthesis occurs. From these statements it can be inferred that any increase in sulphydryl in the cell will cause a tendency to cellular proteolysis or cell decomposition, while a shift in the intracellular SH—SS equilibrium in favor of the oxidized form (SS) will stimulate protein synthesis, a process which appears to be essential for cell division. Whereas protein synthesis and protoplasmic synthesis are not directly synonymous with mitosis, cell multiplication cannot continue for any length of time if this process is not only inhibited, but counteracted, by protein decomposition resulting in cell destruction.

Voegtlin and Mavern expressed similar views in a study of the relation between the oxidation and the proteolysis of malignant tumors. The occurrence of necroses in tumor tissue is explained by them as due to the existence of an inadequate vascular supply and consequently a deficient circulation of blood in parts of the tumor, resulting in insufficient food supply, accumulation of lactic acid and local increase of the hydrogen ion concentration, causing the death of cells. The low oxygen tension and p_H and the stability of sulphydryl thus attained stimulate proteolysis by activation of the tissue proteases. This destructive process can, in the opinion of the two authors, extend to the surrounding tissue, while the products of protein degradation are either removed through the blood or utilized by the adjacent tumor cells for growth and multiplication, a process which will simultaneously also be favorably affected by the increase in intracellular sulphydryl. The conceptions held by Voegtlin and Mavern are essentially identical with those supported by Waldschmidt-Leitz concerning the causative mechanism of tumor necroses and of the destruction of the surrounding normal tissue.

These theories are to a certain extent supported by the observation of Rosenthal and Voegtlin that malignant tissue, the liver and the brain, in contrast with other tissues, keep glutathione for some time in the reduced form. It may also be pointed out that parenchymatous organs which normally have a high glutathione content (liver, suprarenal glands) have a marked tendency to rapid postmortem autolysis. But observations made on isolated dead tissue and on postmortem changes cannot be applied without restrictions to necroses in vivo, which are exposed to the effects of the surrounding living tissue.

Against the validity of these theories numerous objections have been raised. Krebs found that the proteolytic activity of tumor cells is high but within normal limits, while Kleinmann and Werr could not demonstrate in extensive investigations that the catheptic activity of normal

and malignant tissues differs in quantitative or qualitative respects. They concluded, therefore, that no interrelations can be established between increased growth and proteolytic processes in tumors. These results have been substantiated by Malowan and Rondoni. Kleinmann furthermore pointed out that the cathepsin of tumor tissue cannot be activated against its own proteins by the usual method, and that Stern succeeded in this only by means of heavy metal catalysis. This assertion of Kleinmann was, however, disputed in recent investigations of Waldschmidt-Leitz.

Heinlein, contradicting Waldschmidt-Leitz, called attention to the fact that the older portions of the tumor contain not more but less glutathione. Moreover, Morel and Delore and Vosco and Castagna observed that reduced glutathione disappears rapidly from dying and necrotic tissue. Abderhalden noted that the autolysis of minced liver, spleen and kidney is not appreciably influenced by the addition of reduced glutathione, which indicates that proteolysis cannot be stimulated by sulphydryl beyond a certain optimum. Krebs noted that no definite conclusions as to intracellular processes in vivo can be drawn from results obtained with tissue extract, an opinion which was strongly emphasized by Edlbacher also.

The action of sulphydryl on enzymatic activity in vivo and to a certain extent also in vitro is not yet sufficiently understood, as it seems to be difficult to distinguish with present methods between a pseudo-activating effect of sulphydryl on the enzymes by the removal of heavy metal inhibitors (Krebs; Klein and Ziese) and a direct stimulating effect of sulphydryl (Waldschmidt-Leitz) either alone or in the form of a sulphydryl-heavy metal complex (Waldschmidt-Leitz; Salaskin and Solowjew). The great complexity existing in this respect, which makes it extremely difficult to obtain a clear understanding of the interrelations of the various factors present in living biologic material, is shown by the fact that the activation of arginase is controlled, not only by a simple interaction of enzyme and activator, but by the synergism and antagonism of amino-acids and heavy metals (iron and copper) and their various types of valencies (Stern and Michaelis); the amino-acids probably act in this complex process as a reducing agent of the metal, or the latter, for instance ferrous iron, as a protector of sulphydryl from oxidizing agents (Edlbacher). It seems, moreover, to be doubtful if the activation of certain intracellular proteases in vivo depends exclusively on the presence of sulphydryl, as the cells doubtless contain other reducing substances, such as ascorbinic acid, which is accumulated in organs (liver, suprarenal glands) which excel in their glutathione content.

In critical evaluation of these apparently contradictory conceptions and of the evidence presented, attention may be called to the following

points: Necrosis is by no means a constant characteristic of malignant tumors. Proteolytic processes occurring in tumor necroses are evidently secondary to the coagulation of the cell proteins. Rapid proteolysis of necrotic tissue (benign or malignant) is neither constant nor frequent. The majority of infarct necroses after a primary imbibition of the infarcted tissue with extravasated plasma undergo a dehydration process and are slowly lysed in the course of weeks and months by the action of invading leukocytes and phagocytes (Orth). Similar conditions are commonly observed in necrosis of malignant tissue. The proteases liberated from the dead cells and activated by the sulphydryl compounds are therefore often not able to cause any considerable proteolytic changes in the dead tissue in vivo, in contrast to those observed in vitro and in postmortem autolysis. This delayed proteolytic degradation in vivo may be due to different factors. Sulphydryl substances appearing in necrotic tissue are destroyed by the oxidizing action of the plasmatic material entering the necrotic tissue by exudation from the blood vessels, as it has been shown in recent investigations of Hueper and Russell that plasma oxidizes sulphydryl compounds added in the course of a few minutes at a temperature of 37 C. Plasma will also tend, on account of its buffer power, to prevent a shift of the reaction of the necrotic tissue from the alkaline to the acid side, which is more favorable to the stability of sulphydryl compounds and to proteolysis. The blood of tumor carriers has in addition an increased antiproteolytic titer, according to the statement of Wells. There will be, moreover, a drainage of enzymes from the necrotic tissue into the blood owing to the increased permeability of dying and dead cells (Oppenheimer; Mandelbaum). It can also be assumed with some justification that easily diffusible substances, such as the enzymatically important sulphydryl compounds, particularly those not bound to proteins, are relatively rapidly removed by diffusion from the dead tissue (Morel and Delore; Visco and Castagna).

Vascular disturbances and cell crowding in the tumor, together with the increased need for food material for the maintenance and proliferation of tumor cells, resulting in a keen and certainly sometimes unfavorable competition among the tumor cells for these substances, may account for and contribute to the frequency and exaggeration of necrotic processes in tumor tissues. Similar factors are apparently responsible for the degeneration of the normal tissue exposed to the infiltratively growing malignant cells, accounting for their "destructive" action. This conception in regard to "destructive" growth, which is also applied to many benign manifestations, such as inflammatory hyperplasias and endometriosis, is supported by the observations of Rondoni who noted that tumor cathepsin prepared after the method of Waldschmidt-Leitz shows no special features in comparison with the enzyme of normal

tissues. Price demonstrated that in malignant conditions the surrounding normal tissue is not digested by enzymes liberated from the tumor, and that the growth of the tumor does not depend on the autolytic products resulting from the degeneration of the surrounding normal tissues.

It is evident from these data that the intracellular activation of cathepsin in malignant tissue is not responsible for the causation and frequency of necroses and the infiltrative and destructive growth of malignant neoplasms.[1]

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1. This conception has received additional support by the recent work of Maschmann and Helmert, who noted that the presence of much or especially active cathepsin is not a prerequisite for the orderly growth of embryonic cells or for the disorderly growth of malignant cells and that cathepsin does not participate in the autolysis of malignant cells, as they found almost no cathepsin in necrotic tumor tissue from mice. Borger, Peters and Kurz, who investigated the sulphydryl content of infarcted tissue, pointed out that decrease of respiration and increase of proteolysis do not result in necrosis, as Waldschmidt-Leitz had assumed. They observed that the sulphydryl content of necrotic tissue of artificial and spontaneous infarcts decreases rapidly. One hour after ligation of the vessel a decrease in the sulphydryl content of the affected tissue was found, while after from forty-eight to seventy-two hours only 10 per cent of the original sulphydryl content was left. The decrease of sulphydryl in the infarcted tissue was due to oxidation, a process which was favored by the relatively alkaline reaction of the necrotic tissue (p_H 7.1 to 8.4 against a normal p_H of 6.4 to 7). They concluded that a marked action of cathepsin in necroses in vivo is not possible and that thereby the absence of liquefaction in infarcts is satisfactorily explained. These observations and conclusions agree well with the results of recent investigations of Waldschmidt-Leitz and his co-workers on cancer in rats, a work to which Hueper contributed the histopathologic part. The necroses were practically free from cathepsin.

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Notes and News

Ella Sachs Plotz Foundation.—During its tenth year this foundation made twenty-one grants, twelve of which were to scientists outside of the United States. During the present great need for aid, "grants will be given in the sciences closely related to medicine without reference to special fields." The maximum granted will as a rule be less than $500. Applications for grants for 1934-1935 must be in the hands of the secretary, Dr. J. C. Aub, 695 Huntington Avenue, Boston, Mass., before May 1, 1934.

Congratulatory Volume.—Supplement XVI of *Acta pathologica et microbiologica Scandinavica* is dedicated to John Forssman, the discoverer of heterophile antibodies, on his retirement at the age limit from the professorship of general pathology and bacteriology in the University of Lund, Sweden. The supplement covers 611 pages and contains 51 articles by pupils and friends of the dedicatee.

Society News.—At the last annual session of the Society of American Bacteriologists in Philadelphia, Milton J. Rosenau was elected president; Karl F. Meyer, vice-president and James M. Sherman, secretary.

The next annual meeting of the American Association of Physicians will be held at the Chalfonte—Haddon Hall, Atlantic City, May 1 and 2, 1934.

The fiftieth session of the American Association of Anatomists is to be held at the University of Pennsylvania, Philadelphia, March 29 to 31, 1934.

The second annual conference of the Society for the Prevention of Asphyxial Death was held in New York on February 19. In addition to papers on the scientific and practical aspects of asphyxia there was a display of appropriate scientific and technical exhibits.

CORRECTION

In the abstract of an article by Dr. A. Feller and Dr. H. Sternberg (*Virchows Arch. f. path. Anat.* **285**:112, 1932), which appeared at the top of page 111 in the January issue, the name of a syndrome was misspelled. This should be "Klippel-Feil" instead of "Kippel-Weil."

Abstracts from Current Literature

Experimental Pathology and Pathologic Physiology

THE INCISOR TEETH OF ALBINO RATS AND GUINEA PIGS IN VITAMIN A DEFICIENCY AND REPAIR. S. B. WOLBACK and P. R. HOWE, Am. J. Path. **9**:275, 1933.

The initial effect of a deficiency in vitamin A on the incisor teeth of rats and guinea-pigs is on the enamel organ. The ameloblasts respond earliest by atrophy, and then the remainder of the organ atrophies; finally, metaplasia, calcification and, in the guinea-pig, ossification occur. Atrophy and depolarization of odontoblasts follow changes in the enamel organ. The odontoblasts survive longest on the side (labial) in apposition to the enamel organ. In long continued experiments, gross deformities in the incisors of rats resulted from absence or deficiency of dentine formation. Two types of denticle formation are described, one built up by depolarized odontoblasts, the other by inclusions of ameloblasts made by the folding of imperfectly formed dentine at the formative end of the tooth. Defective formation of enamel and other poorly understood conditions in teeth, such as denticles, pulp bone and cementicles, may reasonably be regarded in the human being as possibly due to deficiency of vitamin A. Our observations indicate that in the incisor teeth of rodents the odontoblasts are influenced throughout life by the enamel organ. As in other morphologic problems concerning deficiencies in vitamins, study of the sequences of repair was essential. We emphasize the importance of two types of material for control, the normal and the progressive stages in repair. Our observations indicate that deficiency in vitamin A is the most important of the known vitamin deficiencies in its effect on the formation of teeth.

FROM AUTHORS' SUMMARY.

EXPERIMENTAL PRODUCTION OF RHEUMATIC LESIONS IN THE HEART AND IN THE JOINTS. ERNST VAUBEL, Beitr. z. path. Anat. u. z. allg. Path. **89**:374, 1932.

By repeated subcutaneous or intracutaneous injections of horse serum, morphologic changes were produced in the heart and in the joints of rabbits. In the heart, degeneration of muscular tissue, nodular perivascular cell proliferation and proliferation of the intimal layer of blood vessels were observed. The liver showed degeneration of the parenchyma and proliferation of the reticulo-endothelial tissue. Intra-articular injection of foreign protein caused allergic inflammation of the joints. Periarticular injection produced marked inflammation of all parts of the knee joint. In sensitized rabbits, repeated cooling of the joints may produce severe anaphylactic arthritis with necrosis of the skin. Mechanical injuries of the knee joint may produce in sensitized animals allergic periarticular inflammation. The microscopic lesions of the joints resembled the typical changes of rheumatism in man.

C. ALEXANDER HELLWIG.

EXPERIMENTAL STUDIES ON THE PATHOGENESIS OF JAUNDICE CAUSED BY PHENYLHYDRAZINE, TADASU ITOH, Beitr. z. path. Anat. u. z. allg. Path. **89**:513, 1932.

Adult dogs were given injections of a 5 per cent alcoholic solution of phenylhydrazine. At certain intervals the content of bilirubin in the blood serum and the number of red blood cells were determined. The degree of hemolysis did not correspond to the icteric index. Hemolysis cannot be regarded, therefore, as a cause of the jaundice produced by phenylhydrazine poisoning. After repeated injections of phenylhydrazine, central necrosis of the hepatic cells was observed. These

experiments suggest that phenylhydrazine acts in the same manner as removal of the liver, and that the jaundice caused by this poison is due to retention of bile pigment and not to hemolysis.

C. ALEXANDER HELLWIG.

EFFECT OF ARSENIC ON LYMPHOID TISSUE WITHOUT GERMINAL CENTERS. OTTO ISELI, Beitr. z. path. Anat. u. z. allg. Path. **89**:529, 1932.

In continuation of experiments by von Albertini, Iseli injected arsenic into very young guinea-pigs, in which the lymph nodes are without so-called germinal centers. A single injection of from 1.3 to 1.8 mg. of arsenic produced a diffuse cell degeneration throughout the lymph nodes, whereas lymph nodes with germinal centers show degenerative changes only in the latter. Repeated injections of small doses of arsenic caused only a moderate decrease of lymphoid cells in the lymph nodes without germinal centers. Iseli believes that his experiments corroborate the theory of von Albertini that the so-called germinal centers are protective organs against poisons carried in the blood stream to the lymphoid tissue.

C. ALEXANDER HELLWIG.

EXPERIMENTAL PNEUMONIA. C. KRAUSPE and J. THIESS, Beitr. z. path. Anat. u. z. allg. Path. **91**:276, 1933.

The lobar pneumonias that the authors were able to produce experimentally in normal, immune and sensitized rabbits lead them to conclude that human lobar pneumonia is not a hyperergic inflammation. They believe, however, that variations in the degree of immunity or sensitization at the time of infection by the pneumococcus may be an important factor in determining the variable histologic character of lobar pneumonia in man.

O. T. SCHULTZ.

INFLUENCE OF DIET AND HORMONES ON THYROID FUNCTION. H. PAAL and H. O. KLEINE, Beitr. z. path. Anat. u. z. allg. Path. **91**:322, 1933.

The thyroid function in rats was studied. The object was the preparation of a standard diet that would have no effect on the thyroid gland and on which rats might be maintained for the purpose of studying the effects of other factors on the gland. The salt and vitamin content was kept adequate, and wide variations were made in the proportions of protein, fat and carbohydrate. The thyroids of twenty animals in each series were united and extracted, and the protective action of the thyroid substance against acetonitrile was determined on mice. The thyroids of four animals of each series were examined microscopically. In their histologic studies the authors differentiate between the resting gland with storage of colloid and the active gland with secretion of colloid into the follicle and excretion out of the follicle, either of which processes may predominate over the other. Unbalanced diets activated the thyroid, a high content of protein or fat influencing excretion more than secretion, whereas a diet high in carbohydrate caused secretion to predominate over excretion. Submaximal variations in diet led to the storage of thyroid substance without histologic evidence of activity. Iodine compounds brought glands rendered active by diet into a resting state, the degree of storage depending on the dosage. Thyroxine, the hormone of the urine of pregnant women and extracts of the adenohypophysis activated the thyroid, but when thyroxine and pituitary extract were given together, the former inhibited the activating effect of the latter. Vitamin E deficiency inhibited thyroid activity and diminished the activating effect of extracts of the adenohypophysis. Iodine overcame the inhibiting action of vitamin E deficiency.

O. T. SCHULTZ.

EXPERIMENTAL NONINFECTIOUS ARTHRITIS. DSCHU-YÜ-BI, Beitr. z. path. Anat. u. z. allg. Path. **91**:361, 1933.

In experiments to determine the character of hyperergic inflammation of joints, rabbits received repeated small doses of horse serum. Only when the injections

were made directly into the cavity of the joint did such inflammation of the cartilage and capsule occur. The inflammation was productive in character and resembled that of rheumatic arthritis, but lacked Aschoff bodies and other histologic characteristics of the rheumatic process. The injection into the joint of non-sensitizing liquids, such as water and physiologic solution of sodium chloride, also caused inflammation of the joint.

O. T. SCHULTZ.

EFFICIENCY OF THE KIDNEY IN COMPENSATORY HYPERTROPHY. H. STAHR, Centralbl. f. allg. Path. u. path. Anat. **57**:1, 1933.

The author believes with others that the straight tubules of the kidney are more capable of regenerating than are the convoluted tubules. He presents evidence to prove that a single kidney with compensatory hypertrophy cannot withstand emergencies as well as two normal-sized kidneys. He cites the incompetence of the single enlarged kidney in the following conditions: replacement of one kidney by hypernephroma; agenesia of one kidney; hydronephrosis; stone formation in and destruction of a kidney; disappearance of one kidney due to vascular disease; hypoplasia of one kidney; congenital cystic kidney, and tuberculosis of one kidney.

GEORGE RUKSTINAT.

INJURY TO THE BLOOD VESSELS BY CROTALIN. K. APITZ, Centralbl. f. allg. Path. u. path. Anat. **57**:273, 1933.

Ecchymoses were noted in the mesentery of a mouse from five to ten minutes after it had been painted with a 1:1,000 solution of crotalin. The size of the extravasations and the speed with which they developed were noted through a window in the mesentery. After the mesentery was painted with the poison, the circulation continued, and in from three to five minutes red blood cells escaped from the capillaries. The blood gushed out from arterioles and capillary arterioles with "volcanic" force, so that often the serosa tore. When the serosa remained intact, blood soon spread beneath it to obscure the entire field. Where the circulation was only moderately active, free blood cells occurred in grapelike clusters, and subsequent hemorrhage slowly added more red cells to these. From venous capillaries, single red blood cells were extruded at intervals of about a minute. The bleeding did not seem due to inflammation, because stasis and reversal of capillary flow occurred only after bleeding had taken place.

In frogs, crystals of the poison laid on the mesentery slowed the blood stream in the underlying vessels, but bleeding occurred only after the crystals had dissolved. The bleeding was not increased when the pressure in the mesentery was increased by pressing on it with a glass needle.

Sections of mesentery of rats, mice and guinea-pigs failed to disclose alterations in the endothelium of the blood vessels after varying doses of crotalin had been injected intraperitoneally. The conclusion is reached that crotalin is not primarily cytolytic for endothelium but derives hemoglobin, an activating substance, from the wall of the vessel, and in the proper serum medium exerts its injurious effect.

GEORGE RUKSTINAT.

THE BLOOD FORMATION AND THE COPPER CONTENT OF THE CHICKEN EMBRYO. S. SÜMEGI, Frankfurt. Ztschr. f. Path. **43**:565, 1932.

The copper content of chicken embryos during incubation increases gradually up to the time of the onset of respiration. Beginning from the onset of respiration, the copper content increases more rapidly. The number of red blood cells and their hemoglobin content are in direct proportion to the copper content of the embryo. The morphologic maturity of the blood cells is also in direct proportion to the copper content. Twenty-four hours after the chicken is hatched, the copper reserve is markedly diminished.

O. SAPHIR.

EXPERIMENTAL PRODUCTION OF LEUKEMIA AND LYMPHOSARCOMA IN MICE BY CHRONIC POISONING WITH INDOL. W. BÜNGELER, Frankfurt. Ztschr. f. Path. **44**:202, 1933.

Various doses of a watery solution of indol were injected subcutaneously into a large number of mice. A single injection caused an inhibition of respiration in tissue examined supravitally. Injections over a long period produced, in addition, increased fermentation. Artificially produced foci of regeneration healed readily and did not, as a rule, precede tumor formations. In only three instances, a small papilloma was found. Severe anemia and leukopenia developed in a large number of animals. Autopsy disclosed gelatinous atrophy of the bone marrow and atrophy of the blood-forming organs. Animals which survived these changes revealed later reparative hyperplasia of the blood-forming organs and distinct leukocytosis in the circulating blood. Of 594 mice, only 97 survived after a period of eight months. Aleukemic lymphadenosis developed in 4 of these, in 1 presenting the histologic appearance of a lymphosarcoma. Myelosis developed in 13 of the 97 animals (4 revealed leukemic myelosis and 9 aleukemic myelosis). The remainder of the 97 animals showed, at autopsy, marked atrophy of the bone marrow, spleen and lymph nodes, and sometimes also severe amyloid infiltration in these organs, in addition to much fibrosis. The author believes that the reason why some animals showed anemia and atrophy of the blood-forming organs, and others hypertrophy and tumor formation, lies in constitutional differences. The majority of the 80 remaining animals, however, showed extramedullary blood-forming foci in the liver, spleen and lymph nodes. In blood smears of these animals, leukocytosis was often demonstrated. Because of the tumor-like proliferations in extramedullary blood-forming organs and because of the low respiration and marked formation of lactic acid in the surviving tissues, it is much more likely that leukemia is a tumor rather than a simple systemic hyperplasia of the blood-forming organs.

O. SAPHIR.

EFFECT OF THE HORMONE OF THE SUPRARENAL CORTEX ON THE GENITAL SYSTEM. S. KAPLAN, Frankfurt. Ztschr. f. Path. **44**:302, 1932.

From a series of experiments, the author concludes that the hormone of the suprarenal cortex has an inhibitory effect on the genital system of both the male and the female. The lipoid component of the hormone, however, had, to a slight degree, a stimulating effect on the sex organs of the male.

O. SAPHIR.

INTRATHYROID PARATHYROID TUMOR AND GENERALIZED FIBROCYSTIC OSTEITIS. H. SCHLESINGER and E. GOLD, Klin. Wchnschr. **12**:784, 1933.

The conditions indicated by the title were observed in a woman aged 42. The onset of the disorder was associated with pregnancy. After surgical excision of the parathyroid tumor, the excretion of calcium in the urine diminished transiently to zero.

EDWIN F. HIRSCH.

FUNCTIONATING IPSIHOMOGENEOUS TESTICLE (CAT) TRANSPLANT SURVIVING EIGHT YEARS. B. ROMEIS, Klin. Wchnschr. **12**:1640, 1933.

The surviving tissues were mainly Leydig cells.

EDWIN F. HIRSCH.

BONE CHANGES IN EXPERIMENTAL ACIDOSIS. L. HASLHOFER and R. P. CUSTER, Virchows Arch. f. path. Anat. **289**:332, 1933.

Katase and his co-workers, by the administration to growing young rabbits of an excess of cane sugar in addition to the regular diet, caused osseous changes that they considered similar to those of osteitis fibrosa and that they believed to be the result of acidosis caused by the high intake of carbohydrates. In the experiments here reported, growing rabbits received 3.5 Gm. of dextrose sub-

cutaneously twice daily for periods of from thirty-three to eighty-five days. The primary and essential changes that occurred in the bones were similar to those of human and experimental rickets. The fibrotic changes described by the Japanese observers, the present authors hold to be secondary and the result of mechanical factors acting on the weakened bones.

O. T. SCHULTZ.

EXPERIMENTAL CORONARY SCLEROSIS. W. MOSEBACH, Virchows Arch. f. path. Anat. **289**:647, 1933.

Pfleiderer, working in Schmidtmann's laboratory, showed that it is possible to produce typical atherosclerosis of the coronary arteries in rats by combining the feeding of cholesterol and vitamin D (viosterol) with daily exercising of the animals in a treadmill. The purpose of the present work, which was also done in Schmidtmann's laboratory, was to evaluate the rôle of the three factors, cholesterol, vitamin D and functional activity, in the development of the coronary sclerosis. It was found that neither work alone nor work combined with the feeding of cholesterol caused disease of the coronary arteries. Vitamin D is necessary; it can be replaced by epinephrine but not by irradiation of the animals.

O. T. SCHULTZ.

TISSUE CULTURE OF SYNOVIAL MEMBRANE. E. VAUBEL, Virchows Arch. f. path. Anat. **289**:670, 1933.

After a brief review of the varying opinions that have been and are still held regarding the histologic structure and nature of the synovial membrane and the origin of synovial fluid, the author presents the results obtained by tissue culture. Cultures of serous membranes and other mesenchymal tissues from the same animal, the rabbit, were also studied. Synovial membrane is mesenchymal in origin, but in culture it differs in type of growth and in cell function from other mesenchymal tissue. The actively growing cells are elongated and have a granular cytoplasm, the granules staining deeply with toluidine blue and neutral red. The cells form a syncytial network in which appear spaces formed by plasmolysis brought about by a proteolytic enzyme. About the spaces the cells become polyhedral or cuboidal and may form a closed, regular layer similar to epithelium. The spaces are filled with a mucoid fluid, and the network of tissue with its fluid-filled spaces has the appearance of embryonic mucoid tissue. The fluid is looked on as the ground substance of the synovial tissue. Coalescence of the spaces leads to the formation of the joint cavity. Because of the specialized functions of the growing cells derived from synovial membrane, the author proposes for them the name "synovioblast."

O. T. SCHULTZ.

PHYSIOLOGY OF THE HYPOPHYSIS. J. B. COLLIP, H. SELYE and D. L. THOMPSON, Virchows Arch. f. path. Anat. **290**:23, 1933.

In this article Collip and his associates at McGill University present a succinct and well organized summary of experimental work on the hypophysis that has appeared in briefer form in American and Canadian journals. They describe a method of approach for the removal of the hypophysis through the base of the skull that does not necessitate opening of the pharynx and that they consider superior to other operative procedures. The rat has been the experimental animal. With hypophysectomized rats as the test object, it has been possible to study the effects of various extracts of the pituitary. It has been possible to separate at least three active principles, a growth hormone, a sex hormone and a thyrotropic hormone. Still another principle, which prevents or overcomes the atrophy of the suprarenal cortex which follows removal of the hypophysis, they believe to be distinct from the other three hormones. They present evidence that prolan, the sex hormone isolated from the urine of pregnant women, is not identical with the pituitary sex hormone. In sexually immature rats, prolan causes theca luteinization

of the ovarian follicles but not maturation of follicles or the formation of true corpora lutea, whereas the sex hormone prepared from the pituitary does have the two last named actions. In the male animal, prolan causes hyperplasia of the interstitial tissue of the testis and increase in the size of the accessory sex glands, but does not lead to regeneration of the tubular epithelium. The pituitary sex hormone effects regeneration of seminal epithelium and renewed spermatogenesis. Hypophysectomy during the second half of pregnancy indicates that the pituitary is not necessary for the continuation of pregnancy, the normal birth of the young and the initiation of milk secretion. In such animals lactation, although established, ceases within a few days of the birth of the young. In the normal, nonpregnant female, administration of prolan followed by castration leads to the secretion of milk. If, in such animals, the hypophysis is also removed at the time of castration, lactation does not occur.

O. T. SCHULTZ.

INFLUENCE OF CYTOTOXINS ON THE GROWTH AND METABOLISM OF TISSUE CULTURES. N. N. SPASSKY, Ztschr. f. Immunitätsforsch. u. exper. Therap. **77**:365, 1932.

Two types of cytotoxic serums were employed, one of which was produced by immunizing rabbits with splenic tissue of guinea-pigs; the other was directed against the tissues of chick embryos. Some of the serums arrested or inhibited the growth of the homologous tissues. The cellular metabolism, as measured by the decrease of the sugar content of the culture, was only moderately lowered. This indicates that the damage to the cells of the tissue culture was not very far-reaching and, furthermore, that the amount of energy necessary for the maintenance of vital activities is much greater than the amount consumed for growth.

I. DAVIDSOHN.

QUININE AND ULTRAVIOLET RAYS. O. JÍROVEC and V. BOUŠE, Ztschr. f. Immunitätsforsch. u. exper. Therap. **78**:100, 1933.

The toxicity of solutions of quinine, acriflavine, eosin and pyronine for paramecia did not increase following irradiation of the solutions with ultraviolet rays. This contradicts the reports of Roskin and Romanowa, who had observed à marked increase of the toxic effect of quinine on paramecia following irradiation.

I. DAVIDSOHN.

COMBINED ACTION OF ARSPHENAMINE AND ULTRAVIOLET RAYS ON SPIROCHAETA PALLIDA. S. S. ORLOW and L. B. LEWINSON, Ztschr. f. Immunitätsforsch. u. exper. Therap. **78**:264, 1933.

Rabbits were given combined treatment with arsphenamine and ultraviolet rays after the development of primary syphilitic lesions. The fur on the abdomen was removed and an erythema dose given (usually from three to five minutes at 25 cm.) immediately after the injection of neoarsphenamine and again on the following day. The result was a marked increase in the therapeutic effect and a shortening of the period of illness. The spirochetes in the primary lesion disappeared earlier than in the controls. The toxic effect of the drug was not increased. Orlow and Lewinson advocate a wider application of the combined treatment in the clinic.

I. DAVIDSOHN.

FAMILIAL OCCURRENCE OF LEUKEMIA. SVEND PETRI, Acta path. et microbiol. Scandinav. **10**:330, 1933.

The literature is reviewed, and thirty-three cases of familial leukemia are described, of which eleven are beyond doubt. The lymphatic type occurred in twenty-two instances. There was an average of three cases in a family. The author adds a

report on chronic lymphatic leukemia in two brothers. There is no evidence of hereditary transmission of leukemia, although there is some endogenic factor associated. The presence of infection or of a common external agent could not be ruled out. The possibility of mere coincidence in "familial" leukemia must be considered. Lymphatic leukemia occurred in 85 per cent of related persons, while myelogenous leukemia occurred in nonrelated persons.

JACOB KLINE.

Pathologic Anatomy

CORONARY EMBOLISM. O. SAPHIR, Am. Heart J. **8**:312, 1933.

The literature on coronary embolism is reviewed and the rarity of such an occurrence emphasized. Cases in which the source of the embolism is not found at autopsy should not be accepted as proved cases of coronary embolism. Three cases of coronary embolism are reported. In one, the source of the embolism was a thrombus in the femoral vein; there was also a patent foramen ovale. In the second case, the source of the embolus was a mural thrombus in the right coronary artery, occurring on the basis of an atheromatous ulcer. The embolus had lodged in the distal part of this artery at the origin of the posterior descending branch. In the third instance, the source of the embolus which had occluded the mouth of the right coronary artery was a thrombus occurring on an atheromatous ulcer in the region of the sinus of Valsalva. In all three instances the patients died suddenly.

AUTHOR'S SUMMARY.

MULTIPLE RUPTURE OF THE HEART BY INDIRECT TRAUMA. O. SWINEFORD, Am. Heart J. **8**:418, 1933.

A unique instance of multiple rupture of the heart caused when an automobile struck the patient from behind is presented. One rupture was of the interventricular septum, one was of the anterior wall of the right ventricle and one was of the interauricular septum.

RELATIONSHIP OF THE RHEUMATIC PROCESS TO THE DEVELOPMENT OF ALTERATIONS IN TISSUES. ALVIN F. COBURN, Am. J. Dis. Child. **45**:933, 1933.

The observations at necropsy are presented in six cases of rheumatic fever in the active stage. The diagnosis was established in each instance by the characteristic early specific lesion in the endocardium of the mitral valve and left atrium. The conspicuous lesions, however, consisting of numerous focal hemorrhages in the viscera and beneath the serosal surfaces, might be considered as nonspecific, but are here looked on as specific also. In the lungs were focal areas of vascular engorgement, subpleural and alveolar hemorrhage and massive accumulations of large mononuclear cells. Polymorphonuclear leukocytes were rarely seen, and micro-organisms were not detectable in these lesions. There were no apparent changes in the blood vessels. These anatomic findings indicate that in addition to the well recognized swelling of endothelium and fragmentation of collagen, diffuse hemorrhagic changes may be characteristic of the active rheumatic process.

RALPH FULLER.

CYSTS AND DIVERTICULA OF INTESTINAL ORIGIN. HENRY G. PONCHER and GEORGES MILLES, Am. J. Dis. Child. **45**:1064, 1933.

A case of enterogenous cysts of the mediastinum containing gastric mucosa and an intramesenteric cyst of the ileum containing gastric mucosa is reported. Attention is redirected to the epithelial nodes and diverticula reported by Lewis and Thyng as a probable source of origin for these rare anomalies.

FROM AUTHORS' SUMMARY.

NIEMANN-PICK'S DISEASE AND OTHER FORMS OF SO-CALLED XANTHOMATOSIS. LUDWIG PICK, Am. J. M. Sc. **185**:601, 1933.

The knowledge of the generalized essential xanthomatoses is still recent in its present classification. The important information regarding the nature of Gaucher's, Niemann-Pick's and Hand-Schüller-Christian's diseases dates back only to the last decade. There is, however, no doubt in regard to the principal differences among these three conditions. The separation of these three storage diseases from one another is the more certain because the differentiation is not only clinical and anatomic but also chemical. Gaucher's disease stores mainly kerasin; Niemann-Pick's disease, phosphatides, and Hand-Schüller-Christian's disease, cholesterol. It is true that certain features are common to all three diseases. In particular, there is a familial congenital disturbance of the lipoid metabolism on a constitutional basis, and this aberration shows predilection for the Jewish race. The reason for this is probably the coincidence of the determining hereditary factors favored by frequent blood marriages. All three diseases are accompanied by hemachromatosis with yellowish-brown pigmentation of the exposed skin. In all three diseases, disappearance of the storage cells may occur, with the subsequent formation of fibrous scars. Gaucher's disease and Hand-Schüller-Christian's disease exhibit surprisingly independent localization of lipoid storage within the skeletal system. This occurs apparently in still another form, which is at present still classified among the unnamed essential xanthomatoses. Yet there is, aside from this fundamental agreement, almost always a particular characteristic for each disease entity. Gaucher's disease and Niemann-Pick's disease predominate in the female sex; Hand-Schüller-Christian's disease predominates in the male sex, as far as the existing observations show. In Gaucher's disease and in Niemann-Pick's disease the cicatricial new formations develop in the liver, with disappearance of the storage cells directly by a sort of insidious condensation of the fibrous stroma. In Hand-Schüller-Christian's disease, however, and also in the unnamed xanthomatoses of the bone there is formation of granulation tissue. In Gaucher's disease the osseous form of the disease is exceptional. In Hand-Schüller-Christian's disease and also in the unnamed xanthomatoses of the bone, it is the rule and the leading symptom. In Hand-Schüller-Christian's disease the skull is involved primarily; in Gaucher's disease and in the xanthomatoses of the bone, the entire skeleton.

AUTHOR'S SUMMARY.

TUBERCULOUS VEGETATIONS OF THE TRUNK OF THE PULMONARY ARTERY. P. GROSS, Am. J. Path. **9**:17, 1933.

A third case of tuberculous involvement of the main stem of the pulmonary artery has been described. The tuberculous involvement in this case is the result of the extension of tuberculous lymphadenitis from adjacent lymph nodes to the adventitia and thence to the intima of the pulmonary artery.

AUTHORS' SUMMARY.

MICROINCINERATION STUDIES OF HUMAN CORONARY ARTERIES. D. Y. KU, Am. J. Path. **9**:23, 1933.

The method of incineration was employed in the study of the smaller divisions of the coronary arteries in sixty-two patients ranging in age from new-born infants to persons aged 79. Ash was demonstrated in all, but in variable amounts. The smallest amount was found in the arteries of new-born infants. This amount gradually increased during the first, second and third decades, apparently as a corollary of normal growth. The increase in the amount of ash after the third decade was definite, but was without regularity of progress. This total variation, associated with individual variation, was probably the result of arteriosclerosis in these higher age groups. It was found also that rheumatic fever nodules and leukemic infiltrates increased the amount of ash. The ash of coronary arteries is derived principally from the elastic fibers, but also in small part from the intima, media

and adventitia. This should be regarded as a normal finding, but not of necessity as a precursor of arteriosclerosis. The ash is composed almost entirely of calcium salts, but the manner in which these salts are bound to the elastic fibers is not known. As the quantity of elastic tissue increases normally and as it increases as a part of arteriosclerosis, there is an increase in the amount of ash. It is suggested but not proved that alteration in quantity and quality of elastica may have some bearing on the calcification that occurs in the course of arteriosclerosis.

AUTHOR'S SUMMARY.

METASTATIC CALCIFICATION IN MYELOGENOUS LEUKEMIA. D. A. DESANTO, Am. J. Path. **9**:105, 1933.

A case is reported of metastatic calcification occurring in a young girl whose history indicated that she had had myelogenous leukemia for at least two years. The term is employed to designate a condition in which calcium is mobilized from the depots in the bones and reprecipitated in other tissues of the body, particularly elastic tissues, which are probably physically constituted to favor calcium adsorption and reprecipitation. Calcium deposition is also seen to be favored by any phenomenon which reduces the acidity of the tissue fluid. Hence, metastatic calcification occurs in the tissues in which a change in the alkaline direction likely occurs. Recent evidences mentioned show that the leukemias are rarely associated with osteolytic changes in the skeleton, and this infrequency probably explains the rarity of metastatic calcification as a finding in leukemias. Finally, the identity of this condition with the calcifications occurring after the administration of parathormone and viosterol is reaffirmed.

AUTHOR'S SUMMARY.

AMYLOID DISEASE OF THE KIDNEYS. E. T. BELL, Am. J. Path. **9**:185, 1933.

A study of sixty-five cases of amyloid disease of the kidneys is reported. These are arranged in four groups corresponding roughly with the degree of glomerular involvement. In groups A and B the symptoms are essentially those of the underlying infection, and with few exceptions albuminuria or edema is the only symptom referable to the kidneys. In group C there is some impairment of renal function, and in group D there is evidence of advanced renal insufficiency. Albuminuria is rarely absent, but the amount of albumin does not indicate accurately the extent of the amyloid deposit. Edema is a variable feature with no evident relation to the degree of renal damage. Hypertension is occasionally found in amyloid disease with renal insufficiency. It is probably due to obstruction in the arteriolar and glomerular circulation. Renal insufficiency is a frequent cause of death. It is caused chiefly by amyloid deposits in the glomerular capillaries, but obstruction of the tubules by casts and amyloid deposits in the medulla, around the tubules and in the arterioles, is often an important factor in the production of uremia. In the glomeruli amyloid is deposited on the inner surface of the capillary basement membrane. Endothelial nuclei are frequently displaced inwardly and become scattered through the amyloid. The capillaries usually become greatly distended with amyloid, and they may remain permeable in the presence of massive deposits. The glomerular epithelium degenerates and is desquamated. There is commonly a definite increase of endothelial nuclei in the glomerular capillaries preceding the deposit of amyloid. This is attributed to the underlying infection. It is not sufficiently prominent to be identified with clinical acute glomerulonephritis. Amyloidosis is a special form of renal disease. There is no advantage in classifying it as nephrosis. A sharp distinction between nephrosis and nephritis has not been established. Amyloidosis is a primary renal disease. It is rarely a complication of a preexistent clinical renal lesion.

AUTHOR'S SUMMARY.

SPONTANEOUS RUPTURE OF THE HEART. R. L. BENSON, W. C. HUNTER and C. H. MANLOVE, Am. J. Path. **9**:295, 1933.

Forty cases of rupture of the heart have been collected from nearly 7,000 autopsies in Portland, Ore. One rupture was probably of syphilitic origin. Another, a

dissecting aneurysm of a sinus of Valsalva, was due to endocarditis caused by Streptococcus viridans. The remaining 38 ruptures, although in some instances manifesting evidence of syphilis, were attributable to recent or old thrombosis, embolism or arteriosclerosis of the coronary arteries. AUTHORS' SUMMARY.

THE CELLULAR REACTION IN TUBERCULOSIS OF THE CORNEA. E. R. LONG, S. W. HOLLEY and A. J. VORWALD, Am. J. Path. 9:329, 1933.

Central interlamellar corneal injections of from 0.01 to 0.005 mg. of moderately virulent tubercle bacilli of human type were made in a series of normal and tuberculous guinea-pigs, and normal rabbits and cats. Animals of each kind were killed at six hours, one, three and fourteen days and one month, and the nature and extent of the inflammatory response were determined by microscopic examination. In all cases the first reaction noted was at the limbus, and not at the site of injection. The reaction consisted of an outpouring of polymorphonuclear leukocytes from the marginal vessels. It was most intense in the tuberculous guinea-pig (tuberculin reaction), less in the normal guinea-pig, still less in the rabbit and least in the cat. The first cellular reaction at the site of injection in the center of the cornea consisted of leukocytes migrating in from the margin. The reaction was well developed in all animals at twenty-four hours, and the cells taking part were almost exclusively polymorphonuclear leukocytes. After twenty-four hours there was a gradual increase in the proportion of large mononuclears in the reaction. The rate of increase rose with the closer approach of blood vessels, as vascularization of the cornea developed. The paucity of these cells at the earlier stages and the abundance in the vascularized state of the cornea seemed good evidence that the large mononuclear leukocyte in corneal tuberculosis is not locally derived, as formerly claimed. In all animals the large mononuclears, as they reached the site of infection, engulfed the polymorphonuclear leukocytes already there, taking over the tubercle bacilli contained by the latter cells. During the period from three days to two weeks after the injection the inflammatory reaction progressed most rapidly in the tuberculous guinea-pigs, and less rapidly in the normal guinea-pigs, rabbits and cats in the order named. Ulceration occurred in the tuberculous guinea-pigs in two weeks, and these animals were dropped from the series at this point. At one month, the time of the last examination, the intensity of inflammatory reaction, as determined by the size of the lesion and the proportion of the cornea involved, was greatest in the guinea-pig, less in the rabbit and least in the cat. This order is in inverse relation to the general resistance of these animals to the strain of tubercle bacillus used. AUTHORS' SUMMARY.

THE ORIGIN OF THE EPITHELIOID CELL IN TUBERCULOSIS OF THE CORNEA. E. R. LONG and S. W. HOLLEY, Am. J. Path. 9:337, 1933.

Infection of the center of the rabbit cornea with tubercle bacilli of human type resulted in a lesion characterized almost solely by polymorphonuclear leukocytes until the arrival of new capillaries, when a rapid replacement of the polymorphonuclears by mononuclear phagocytic cells occurred. When two infecting doses were placed in the same cornea, one at the margin near the normal blood supply and one in the normally avascular center, the replacement of polymorphonuclears by large mononuclears occurred weeks earlier in the lesion close to the limbus. The mononuclears accounting for this replacement and functioning in the subsequent development of the lesion apparently arose from primitive smaller mononuclear cells present in large numbers in and around the walls of the new capillaries. The source of these cells could not be determined with absolute certainty, but the following observations were evidence that most of them came from the blood stream: Cells of similar character were present among the erythrocytes in the lumens of the blood vessels in great excess of the normal proportion; migration figures of similar cells could be seen in the walls of the growing capillaries, and mitotic figures among them were rare. The primitive cells, after accumulating

in and around the walls of the capillaries, underwent a progressive transformation by simultaneous increase in size and change of character, without mitosis, into epithelioid cells.

AUTHORS' SUMMARY.

FIBROSIS OF THE UTERUS. A. B. BAKER, Am. J. Path. **9**:369, 1933.

With the advance of age, there occurs within the uterine wall a gradual increase of collagenous fibers that ultimately replace the greater part of the muscle. Neither localized nor acute systemic processes have any effect on the uterine wall. Chronic diseases have no effect on the uterine wall of young nulliparas, but hasten the fibrotic process in older nulliparas. The uterine arteries show less pronounced change with age than the uterine muscles. The three alterations most commonly found are medial fibrosis, medial calcification and intimal atherosclerosis. There is no satisfactory evidence that either fibrosis of the uterine wall or increase in elastic tissue following pregnancy is responsible for uterine hemorrhage.

AUTHOR'S SUMMARY.

SEVEN PREHISTORIC AMERICAN SKULLS WITH COMPLETE ABSENCE OF AN EXTERNAL AUDITORY MEATUS. A. HRDLICKA, Am. J. Phys. Anthropol. **17**:355, 1933.

Complete congenital absence of the external auditory meatus and of the tympanic bone was observed in seven skulls of pre-Columbian or old American aborigines. These are the first cases of this nature recorded in persons of this race. The anomaly predominates in females, at least five and probably six of the seven subjects having been of that sex; it is unilateral in all the specimens, and in every one of the seven skulls it exists on the right side. Five of the skulls are from the coast of Peru; one is from a mound in Arkansas, and one from a cave in New Mexico. Two of the five Peruvian skulls come from one moderate-sized burial ground, which suggests close relationship. The anomaly, serious as it is, has produced remarkably few effects on the base of the skull; yet some effects are visible. One of these is a perceptibly smaller development in nearly all of the skulls of the petrous portion on the affected side; another is the absence of the styloid process on the side of the defect in most of the skulls; the third is the presence on the abnormal side, in about the midst of the glaserian fissure, of one or two canals, in some cases of fair size, which are absent on the sound side. The left meatus, while of normal conformation in all the cases, in the majority is of submedian capacity, and in one skull, that of a child, its lumen is decidedly subnormal. The anomaly presented by the specimens here reported can be characterized, it seems, only as "agenesis," due either to some germinal defect or to a weakened influence of the trophic nerve centers. It shows such similarity in the relatively large series of cases here reported that it must be regarded not merely as a chance condition, but as a definite syndrome or unit of agenetic nature.

CONGENITAL CYSTIC DISEASE OF THE LUNG. WILLIAM C. POLLOCK and HORACE P. MARVIN, Am. Rev. Tuberc. **27**:59, 1933.

Congenital cystic disease of the lung is believed to be a definite disease entity of rare occurrence. The cystic condition is secondary to a congenital narrowing of the main bronchus or bronchi of the involved lobe or lobes. The cystic changes are usually more or less stationary, but may be progressive under certain conditions. Usually there is only a congenital defect of the bronchus of one lobe, more frequently the upper lobe. In these cases there may be extensive cystic changes of the entire lobe without symptoms. When more than one lobe is involved, conditions of pulmonary stress by hyperphysical activity may cause a progression of

the cystic disease until such symptoms as dyspnea and cough develop. Cystic disease is usually discovered accidentally by routine examinations. It should not be confused with congenital bronchiectasis, as there are no dilatations of the bronchi of the cystic lung.

H. J. CORPER.

NOCARDIOSIS CUTIS GANGRENOSA. W. H. GUY and T. R. HELMBOLD, Arch. Dermat. & Syph. **27**:224, 1933.

Nocardia was found in blood and tissue culture from a patient with a fulminating gangrenous lesion of the breast. Histologic section showed parenchymatous and interstitial edema in the dermis, with a few polymorphonuclear leukocytes. The deeper vessels were thrombosed. There was a wide zone of perivascular infiltration comprised predominately of polymorphonuclear leukocytes with a scattering of lymphocytes, monocytes and plasma cells. A moderate diffuse infiltration of the same character was present in the papillary zone. Minute foci of coagulation necrosis of collagen occurred throughout the section. The elastic tissue was swollen but not disarranged. Gram-Weigert preparations revealed foci of filaments of Nocardia near the vessels, and, in one instance, in a thrombosed vessel. The patient had lost 60 pounds (27.2 Kg.) prior to the onset of the dermatosis. Bloody diarrhea was present, with ulceration of the rectum and sigmoid. The condition was interpreted as an embolic process with dissemination by way of the blood stream, perhaps in this case from the gastro-intestinal tract.

S. W. BECKER.

SUBCUTANEOUS FAT NECROSIS OF THE NEW-BORN. HOWARD FOX, Arch. Dermat. & Syph. **27**:237, 1933.

Five cases are reported of localized induration of the subcutaneous tissue in young infants, presumably following trauma subsequent to forceps delivery or to violent measures for resuscitation. The lesions persist for from five weeks to five months and disappear. The disease involves the entire subcutaneous tissue, sparing the epidermis and dermis. The process is essentially a necrosis of the fat cells and an infiltration of epithelioid and giant cells. Needle-like crystals in the form of rosettes or sheaths, possibly composed of fatty acids, are found in the fat cells and in the giant cells. The picture is that of a lipophagic granuloma which undergoes, first, cicatricial organization, and, later, complete restitution to the normal condition with the formation of new fat. The condition must be distinguished from sclerema adiposum, sclerema edematosum and scleroderma. Sclerema and scleroderma are much more serious diseases, although many cases in the literature prior to the last decade reported under these names were probably cases of subcutaneous fat necrosis.

S. W. BECKER.

LOCALIZATION AND DEVELOPMENT OF THE MELANIC CELLS OF THE HUMAN CEREBELLUM. J. ARANOVICH, Semana méd. **2**:927 (Sept. 28) 1933.

Aranovich states that in the lateral region of the fourth ventricle in the cerebellum of the human being there exists a nucleus of melanic cells, the so-called subependymal-laterocerebellar nucleus. The nucleus is pigmented during the first months of life and presents morphologic differences from the cells of the locus caeruleus and from those of the locus niger. Under normal conditions, the cells of the nucleus are large and rich in pigment and have a well defined nucleus and nucleolus. Similar to other melanic cells, those of the laterocerebellar nucleus undergo characteristic changes in the course of Parkinson's disease (reduction and deformation of the cells, decrease of the pigment, deformation of the nucleus and disappearance of the nucleolus). The clinical and anatomicopathologic study of a case of Parkinson's disease is reported.

Pathologic Chemistry and Physics

A Reducing Substance in a Chromophilic Adenoma and in the Normal Anterior Pituitary. T. J. Putnam and H. B. Wilcox, Am. J. Path. **9**:649, 1933.

A substance reducing methylthionine chloride, U. S. P. (methylene blue) has been demonstrated in the normal anterior lobe of the pituitary gland and its extract, and in larger amounts in a chromophil adenoma. None was found in a chromophobe adenoma.

Authors' Summary.

Melanogenesis with Reference to Sulphydrils and Protamines. H. J. Ropshaw, Am. J. Physiol. **103**:535, 1933.

The experiments reported here support the view that melanogenesis is an intracellular process and a physiologic function of the pigment cell. It results from the reaction of cystine on protamine, and so in the skin is limited to the epithelial layer — the only one which contains sulphydril compounds. Formation of melanin is an evidence of a phase of nuclear metabolism — the cleavage by which protamine is freed to diffuse into the cytoplasm, with the cystine-cysteine complex serving as an indicator of this reaction. In the cytoplasm the cystine is present within glutathione, and the protamine in the chromatin. Both are freed by enzyme cleavage and react to form melanin when brought in contact. A similar reaction takes place in vitro, progressing rather slowly because of the gradual oxidation of cysteine. It does not occur in an oxygen-free medium, and apparently requires the presence of iron as a catalyst—found in the skin in the protamine. The black precipitate formed in these circumstances becomes white in time, which suggests that melanin may be excreted as colorless succedaneous products. Acidity prevents the reaction, and Ropshaw suggests that there may be a relation between this and albinism.

H. E. Eggers.

The Question of a Pressor Substance in the Blood in Essential Hypertension. G. E. Wakerlin and H. D. Bruner, Arch. Int. Med. **52**:57, 1933.

The action of thirty blood serums from patients with essential hypertension and of fifteen serums from patients with normal blood pressure on the tone of arterial segments from the mesenteric arteries of cattle was studied. No significant differences were found in the vasoconstricting properties of these serums. The results suggest that there is no peripherally acting pressor substance in the blood of patients with essential hypertension. Some evidence was obtained for the residence of a spontaneous rhythmic motor activity in arterial musculature deprived of its extrinsic innervation.

Authors' Summary.

Minerals in Silicotic Lungs. W. R. Jones, J. Hyg. **33**:307, 1933.

The bulk of the mineral residue found in the lungs examined consisted of minute fibers of sericite, a hydrated silicate of aluminum and potassium. The same mineral was found in the rock dust inhaled. Silica in the uncombined state, quartz, was also found in the residue. However, silica in the uncombined state was not the chief cause of silicosis in these cases. The fibrous minerals present seemed to have hastened the process of silicosis, and their presence in the rock appears to be of more importance than the presence of the quartz.

Edna Delves.

A Urinary Compound of Albumin, Bence-Jones Protein, Pseudoglobulin and an Unknown Antigen. W. H. Welker and L. Hektoen, J. Infect. Dis. **53**:165, 1933.

The urine of a patient with myeloma contained a compound of albumin, pseudoglobulin and Bence-Jones protein and an unknown antigen. The Bence-

Jones protein could not be separated from this compound in pure form by boiling or by attempts at crystallization. Individual precipitins in rabbit serum prepared against the compound and against solutions of substances obtained on attempts at crystallization were removed by specific adsorption. AUTHORS' SUMMARY.

ESTIMATION OF TISSUE PHENOLS. M. I. SMITH, Pub. Health Rep. **48**:1487, 1933.

A method has been described for the quantitative estimation of true phenols, free and conjugated, applicable to all body tissues and fluids. The tissues of the normal rabbit (oat and cabbage diet) were found to contain less than 1 mg. per hundred grams of tissue and usually not much over 0.5 mg. of what might be regarded as true phenols. In phenolorthocresol poisoning, phenols were found in appreciable amounts in all the tissues examined. In acute lethal poisoning, free phenol was found in concentrations ranging from about 7 to 26 mg. per hundred grams of tissue, the lowest value being found in skeletal muscle and the highest in the kidney. Conjugated phenols were not found in appreciable amount anywhere. In subacute poisoning, conjugated phenols were found in all the tissues examined, with the exception of the central nervous system, which showed little or no combined phenols. These observations suggest that the function of phenol conjugation is not limited to any one tissue, although it seems to occur predominantly in the kidney, liver and intestine, while the brain and probably also the spinal cord appear to be devoid of this function. As much as from 6 to 8 mg. of free phenol per hundred grams of tissue was found in the central nervous system of the rabbit following the administration of a toxic but nonfatal dose of phenol. AUTHOR'S SUMMARY AND CONCLUSIONS.

IMMUNOLOGY OF CASEINS. M. L. DEMANEZ, Arch. internat. de méd. exper. **8**:233, 1933.

Biologic tests of the caseins from cows, goats and ewes indicate a great similarity in the immune reactions. The caseins of women and mares are quite distinct from the preceding varieties. Casein is a mixture of several proteins, which cannot be distinguished in biologic tests. The specificity of casein is not modified by heat or the action of iodine. In this it differs from protein of blood serum. JACOB KLEIN.

SPECIFICITY OF FIBRINOGENS. M. L. DEMANEZ, Arch. internat. de méd. exper. **8**:255, 1933.

There has been a divergence of opinion as to the immunologic properties of the fibrinogens of the different mammals. By precipitin and absorption tests, the author has tested the fibrinogens of the pig, horse, sheep and cow, and concludes that the fibrinogens of different zoologic species possess only a limited specificity. JACOB KLEIN.

HISTOCHEMICAL AND MINERALOGICAL ANALYSIS OF DUST PARTICLES IN PNEUMONOCONIOSIS. K. F. SCHEID, Beitr. z. path. Anat. u. z. allg. Path. **89**:93, 1932.

For identification of dust particles in fifty lungs, these methods were used: examination of frozen sections of fresh tissue, incineration at from 450 to 500 C., tests with chemical reagents (acids, alkalis), refractometric methods and polariscopy. The characteristics of carbon, graphite, magnetite, pyrite, hematite, lime, silicon dioxide and muscovite are described. From the biologic point of view, two forms of dust must be distinguished: (1) minerals which are readily dissolved by the tissue like lime and siderite and (2) minerals which are deposited in the tissue (silicon dioxide, carbon, rutile and glimmer). C. ALEXANDER HELLWIG.

SPHERICAL MICROLITHS OF BILE. G. LEMMEL and W. BÜTTNER, Beitr. z. path. Anat. u. z. allg. Path. **91**:19, 1933.

Microscopic formed particles of variable size, shape, structure and composition were described many years ago in the bile of the gallbladder. Only recently have these microliths begun to attract attention in the current literature. The authors limit their discussion to the spherical microliths, the morphology of which they describe and illustrate by photomicrographs. These microliths have a laminated and often radially striate structure. The smallest ones have a small center and a highly refractile outer portion, and are light green. Larger ones are darker and consist of layers of refractile ground substance separated by thinner layers of bile pigment. The authors interpret the increase in size and the lamination as evidences of growth and age. The presence of older microliths may, therefore, indicate pathologic alterations in the biliary passages that are no longer evident at the time of examination. Older microliths may show the effects of the action of bile on their superficial portions.

O. T. SCHULTZ.

QUANTITATIVE SPECTROGRAPHIC DETERMINATION OF GOLD IN TISSUES. WERNER GERLACH, K. RUTHARDT and L. PRÜSENER, Beitr. z. path. Anat. u. z. allg. Path. **91**:617, 1933.

Gerlach's seventh contribution to the elementary chemical analysis of tissues is devoted to gold. There is described a spectrographic method that permits rapid quantitative as well as qualitative estimation of gold. Similar methods for copper, lead and manganese are promised. The advantages and possibilities of the spectrographic method are discussed. For the histochemical detection of gold in tissues, the method of Timm was found to be best, but it failed to reveal small quantities that could be readily determined by the method of spectral analysis.

O. T. SCHULTZ.

HYPERPROTEINEMIA IN MYELOMA. M. BÖNNINGER, Deutsche med. Wchnschr. **59**:770, 1933.

A 52 year old man who was ill with generalized myeloma was found to show a marked tendency to coagulation of the blood. This was so extreme that it was impossible to count red cells with Hayem's solution (mercuric chloride, 0.5 Gm.; sodium sulphate, 5 Gm.; sodium chloride, 1 Gm., and distilled water, 200 cc.). The serum was thick and tenacious like acacia, and the blood corpuscles were markedly clumped. There was an increase of the euglobulin in the serum. The urine contained traces of albumin and no Bence-Jones protein. JACOB KLEIN.

EFFECT OF X-RAYS ON THE LUNGS AND HEART. M. I. KARLIN and B. N. MOGILNITZKY, Frankfurt. Ztschr. f. Path. **43**:434, 1932.

The authors believe that too little attention is paid to the possible damage of vital organs in cases of prolonged roentgen treatment of carcinoma of the mammary glands, lungs and other organs. In reviewing the literature, they found a divergence of opinion concerning this possibility. In dogs that were treated with various doses of roentgen rays, peribronchial and perivascular connective tissue proliferations and epicardial thickenings were found. Bronchopneumonia and necrotizing bronchitis were also encountered. Occasionally hemorrhages were seen, especially pronounced in the perivascular spaces and beneath the endocardium. The authors conclude that possible damage of the heart and of the lungs in the human being treated with roentgen rays over a long period of time must be considered.

O. SAPHIR.

INCREASE IN PHOSPHATIDE IN NIEMANN-PICK'S DISEASE. E. EPSTEIN, Klin. Wchnschr. **12**:56, 1933.

The saturated and unsaturated phosphatide contents of the spleen, liver and brain cells are greatly increased over the normal in Niemann-Pick's disease. In the brain and liver there is a marked increase in the ratio of free cholesterol to cholesterol ester.

D. O. ROSBASH.

SYNTHESIS OF URIC ACID IN BIRDS. W. SCHULER and W. REINDEL, Klin. Wchnschr. **12**:1479, 1933.

The precursors in the synthesis of uric acid in pigeons and geese are found in the liver. Their formation is an enzyme process with an optimum temperature of 41 C. and an optimum p_H of 7.6. The nitrogen sources of the precursors are amino-acids above ammonia but not beyond urea. Precursors may be extracted from muscle, but a fermentation formation has never been demonstrated. The formation of uric acid in the kidney is optimum at p_H 7.1.

AUTHORS' SUMMARY.

DETECTION OF THORIUM IN TISSUES. W. GERLACH, Virchows Arch. f. path. Anat. **287**:135, 1932.

The author gives a brief discussion of the spectrographic detection of thorium in tissues. The thorium lines, at 2,832 and 2,837 angstrom units, are easy to detect because they lie between the prominent magnesium lines that all tissues give.

O. T. SCHULTZ.

DISTRIBUTION OF IMMUNE BODIES IN THE PROTEIN FRACTIONS OF THE SERUM. A. A. SCHMIDT and KLARA TULJTSCHINSKAJA, Ztschr. f. Immunitätsforsch. u. exper. Therap. **79**:311, 1933.

The proteins of the serum were precipitated with a saturated solution of ammonium sulphate. Agglutinins of the typhoid bacillus were present predominantly in the euglobulin fraction and to a lesser degree in the pseudoglobulin fraction. Antisheep hemolysins of rabbit serums and complement-fixing antibodies of human syphilitic serums were found almost entirely in the euglobulin fraction. The albumin fraction did not contain any of the mentioned antibodies.

I. DAVIDSOHN.

CHEMICAL EXAMINATION OF THE SPLEEN IN GAUCHER'S DISEASE. H. MAI, Ztschr. f. Kinderh. **55**:12, 1933.

The spleen from a person with Gaucher's disease was examined chemically and found to contain from 8 to 9 per cent kerasin. The sterin and phosphatide content was less than normal. A normal spleen examined by the same chemical method showed no noteworthy amount of cerebrosides. The chemical examination confirmed the clinical diagnosis of Gaucher's disease.

JACOB KLEIN.

Microbiology and Parasitology

BLOOD CULTURES IN CHRONIC ARTHRITIS. E. F. TRAUT, J. Infect. Dis. **52**:230, 1933.

Seventy-one per cent of thirty-eight patients with chronic arthritis yielded primarily bacillary or diplococcic forms in forty-one instances and coccoid forms in chains in three instances. These bacteria had the characteristics of enterococci. On isolation the earliest colonies resembled the G colonies of Hadley. The essentials of successful blood cultures in chronic arthritis are prolonged cultivation, faultless technic, suitable culture mediums and the recognition of pleomorphism and dissociation.

AUTHOR'S SUMMARY.

HEMOGLOBINOPHILIC BACILLI FROM INFANTILE MENINIGTIS. B. E. EDDY, J. Infect. Dis. **52**:242, 1933.

The gram-negative hemoglobinophilic bacilli of infantile meningitis grew most luxuriantly on blood agar when first isolated from the spinal fluid. Apparently some constituent of the spinal fluid is especially favorable for their growth. All strains required blood in the medium even after two years' artificial cultivation. All strains examined produced indol, and a medium to which tryptophan was added was found to enhance growth greatly. The sugar fermentations of the hemoglobinophilic bacilli confirmed the observation of Rivers and Kohn with the exception of one strain. All of the strains of hemoglobinophilic bacilli studied were uniformly pathogenic for young white rats and nonpathogenic for chickens.

AUTHOR'S SUMMARY.

PLEOMORPHIC ORGANISM SHOWING RELATIONSHIPS BETWEEN STAPHYLOCOCCI AND ACTINOMYCETES. M. V. NOVAK and A. T. HENRICI, J. Infect. Dis. **52**: 253, 1933.

A yellow staphylococcus was recovered from triturated, Berkefeld-filtered cultures of an actinomycete after incubation for five weeks at room temperature. This organism was culturally and morphologically identical with staphylococci on ordinary routine mediums. On dextrose agar, rods and branching filaments developed from the coccoid forms. Filaments or rods reverted to cocci when transferred again to plain agar. Smooth and rough colonies were obtained from cultures of the yellow staphylococcus. Rods and coccoid forms appeared in both smooth and rough colonies. A G type culture was obtained from aged broth cultures of the organism. The elements in the G culture ranged in size from very minute to normal. These G forms demonstrated no filamentous properties and were strictly bacterial in nature. It is suggested that the observations support the theory that the staphylococci are related to the actinomycetes.

AUTHORS' SUMMARY.

BACTERIOLOGIC INVESTIGATION OF THE BLOOD IN RHEUMATIC FEVER. B. R. CALLOW, J. Infect. Dis. **52**:279, 1933.

Diplostreptococci (alpha type) and pleomorphic bacilli may be recovered repeatedly from the blood of patients with rheumatic fever and certain diseases mostly of the upper respiratory tract. These organisms apparently represent stages in the life cycle of the same organism. A specific etiologic relationship between these organisms and rheumatic fever is questioned.

AUTHOR'S SUMMARY.

DIFFERENTIATION OF BOVINE AND PORCINE STRAINS OF BRUCELLA ABORTUS BASED ON DISSOCIATION. B. S. HENRY, J. Infect. Dis. **52**:403, 1933.

A method for the differentiation of strains of Brucella abortus of bovine from those of porcine origin, based on the size relations of the R and S colonies in the two strains, is presented. In the porcine strains the R colonies are smaller than the S colonies, whereas the reverse is true in the bovine strains.

AUTHOR'S SUMMARY.

THE BIOLOGY OF THE FERMENTING SARCINAE. J. SMIT, J. Path. & Bact. **36**: 455, 1933.

The occurrence of different fermenting sarcinae (brought together into the genus Zymosarcina) in natural materials has been studied, and the morphology and biology of these forms are dealt with. The sugar metabolism of Zymosarcina ventriculi and Zymosarcina maxima has been examined. Comparison of their vitality in pure cultures with that under natural conditions leads to the view that the coccal form of sarcinae represents a sensitive form of the organism which dies

out in a few days, and grows out irreversibly from a stable form, in which sarcinae universally occur and keep alive for long periods in natural materials like soil, sand and bran of cereals. The external shape of this form has not up to now been determined.

AUTHOR'S SUMMARY.

THE PHOTODYNAMIC ACTION OF METHYLENE BLUE ON BACTERIOPHAGE. J. R. PERDRAU and C. TODD, Proc. Roy. Soc., London, s. B **112**:277, 1933.

The concentration of 1:100,000 of methylthionine chloride, U. S. P. (methylene blue) in a broth filtrate of a bacteriophage specific for Staphylococcus krueger produced the complete inactivation of the lytic principle on exposure to light for eight minutes. This phenomenon did not take place in the absence of oxygen. Other strains of bacteriophage which were examined were less susceptible. Higher concentrations of methylthionine chloride were less effective, probably because of the absorption and loss of light in the upper layers of fluid. The inactivating action of the light employed was limited to the wavelengths absorbed by a solution of methylthionine chloride. Attempts to reactivate the bacteriophage by reduction were not successful. A protecting action by the corresponding living organism was observed. Killed organisms had no such effect. The protective action was not strictly specific as it was exhibited by certain heterologous bacteria.

L. E. SHINN.

THE PHOTODYNAMIC ACTION OF METHYLENE BLUE ON CERTAIN VIRUSES. J. R. PERDRAU and C. TODD, Proc. Roy. Soc., London, s. B **112**:288, 1933.

The viruses of vaccinia, herpes, fowl plague, thorter ill, Borna disease, Fujinami's tumor and canine distemper, in cell-free fluids, were inactivated by a concentration of 1:100,000 of methylthionine chloride, U. S. P. (methylene blue) on suitable illumination for a few minutes. The viruses of foot and mouth disease and of infectious ectromelia were more resistant. As with bacteriophage, oxygen was essential for the inactivation. The viruses of herpes, Borna disease and fowl plague were protected by the presence of living cells from the infected animal. Only a slight protection was observed in the case of vaccinia and no protection in the case of thorter ill. The development of the specific lesions of vaccinia and herpes could be prevented by suitable treatment with methylthionine chloride and light within from twelve to twenty-four hours after inoculation.

L. E. SHINN.

TUBERCULOUS BACILLEMIA. JOHN CRIBBIN, Tubercle **14**:163, 1933.

From 190 tubes inoculated with blood according to Löwenstein's method, and in addition on Holm and Schwabacher's mediums, obtained from 17 cases of advanced pulmonary tuberculosis, no positive results were obtained. The patients had advanced cases with repeatedly positive sputum and well marked and severe toxic symptoms. Most of the patients died within from one to five months from the commencement of the investigations; only four are still alive.

H. J. CORPER.

TUBERCULOUS BACTEREMIA. J. TROISIER, T. DE SANCTIS MONALDI, R. CATTAN and MME. KOURILSKY, Ann. Inst. Pasteur **49**:614, 1932.

With the Loewenstein technic for the cultivation of tubercle bacilli from the blood stream, organisms were recovered "in the course of nontuberculous infections," viz., a streptococcic septicemia, an acute pneumonia that was cured without sequelae and a meningococcic meningitis. The organisms were of the human type, thereby excluding avian organisms from the eggs used in the culture medium. It seemed probable that these organisms arose from latent foci, which might mean either apathogenicity or the origin of active processes.

M. S. MARSHALL.

SYPHILIS IN GUINEA-PIGS. J. VAN HAELST, Ann. Inst. Pasteur **49**:778, 1932.

Inoculation of guinea-pigs with material rich in spirochetes was successful, lesions appearing in four weeks and lasting from two to eight weeks. The lesions, especially after several passages, consisted of papules, nodules and ulcerations, rich in organisms and keratitic, which may have been metastatic. The author prefers for the present to consider syphilis as a localized disease in this animal.

FROM AUTHOR'S CONCLUSIONS.

CATARACT IN RABBITS EXPOSED TO HERPES. S. NICOLAU and MME. L. KOPCIOWSKA, Ann. Inst. Pasteur **50**:117, 1933.

"In résumé, four cases of cataract were observed in rabbits during the course of immunization or in rabbits already immunized against herpes virus, of which one appeared to illustrate the fortuitous localization of the organism in the crystalline lens, since the opacification in this case appeared at the peak of the disease. In the other three cases, on the contrary, the cataract could probably be interpreted as trophic trouble at a distance, consequent on changes in the nerves. However that may be, we have thought it of interest to report these cases which may perhaps suggest the origin of certain human cataracts, in which a neurotropic virus is involved in provoking nerve lesions."

SPONTANEOUS TUBERCULOSIS IN ANIMALS. A. CALMETTE, Ann. Inst. Pasteur **50**: 148, 1933.

Spontaneous tuberculosis in rabbits and guinea-pigs has been observed from Koch's time to date. A review of the literature, combined with the extensive work with B C G vaccine, has given the author many data for observing the practical aspects of this problem and the dangers in experimental work with tuberculosis. Virtually all stages of tuberculosis appear to occur frequently, some so delayed that they frequently are not observed. This fact explains the individual differences observed in animals housed together, all tuberculous, and some showing a type of infection much different from others. There is no fundamental difference between the guinea-pig, the rabbit and other susceptible animals and man with regard to this infection.

M. S. MARSHALL.

BLOOD CULTURE OF TUBERCLE BACILLI. E. LÖWENSTEIN, Ann. Inst. Pasteur **50**:161, 1933.

A method of blood culture, used extensively by the author in Vienna, consists of a rather complete concentration method, starting with citrated blood, and finally inoculation of a medium consisting of eggs, asparagine solution, potatoes, congo red and malachite green. Organisms were cultivated from various forms of tuberculosis, from acute and chronic polyarthritis, from early cases of chorea and even from patients with dementia praecox.

M. S. MARSHALL.

THE TUBERCULOUS ULTRAVIRUS. G. SANARELLI and A. ALESSANDRINI, Ann. Inst. Pasteur **50**:167, 1933.

Some of the general conclusions by the authors from an exhaustive study of the so-called ultravirus by the collodion sac method are: The ultravirus passed collodion filters in vivo and in vitro. The pathogenicity of filtrates made either way was too weak to cause nodule formation. Cultivation was accomplished, though not easily, by using the pulp of organs of animals of the second or third passage. The peritoneal cavity of animals infected through a sac revealed bacterial forms, "tuberculous protogens." From these forms, on proper medium, developed typical tubercle bacilli, but cultures were frequently sterile. Such recovered organisms were feebly pathogenic, but by repeated growth recovery of virulence was rapid.

Inoculation of guinea-pigs with protogens resulted in characteristic, chronic, fatal processes, with inflammatory or caseogenous anatomic changes, absence of visible tuberculous granulomas, and the frequent presence of acid-fast rods. The idea of the existence of a complex cycle in the life of the organism was considered to be confirmed.

M. S. MARSHALL.

NEW STUDIES IN EXPERIMENTAL SYPHILIS. C. LEVADITI, A. VAISMAN, M. R. SCHOEN and J. G. MEZGER, Ann. Inst. Pasteur **50**:222, 1933.

In an extensive report three phases of the subject are considered. Regarding the question of whether Spirochaeta pallida is only one visible phase of a complex cycle, it is stated: "Although new investigations are necessary to complete our knowledge of the evolutionary cycle of the syphilitic virus, one may admit as very plausible, without being definitely demonstrated, the concept of the existence of an infravisible phase in the evolution of Spirochaeta pallida." This chapter serves as a preface to a study of neurosyphilis in monkeys and rabbits, with careful histologic study, in which evidence was found that cyclic phases of strains, some more neurotropic than others, occurred in the parenchyma of the nerve. The third point at issue concerns the possible avirulence of the "pale spirochete" in the spirochete stage: "The preceding observations, added to those recently reported by Jahnel, Prigge and Rothermundt, make us hesitate to subscribe to the concept of the avirulence of the pale spirochete, ingenious and original as it may be."

M. S. MARSHALL.

THE DOG AND THE "BUTTON FEVER" VIRUS. PAUL DURAND, Arch. Inst. Pasteur de Tunis **21**:239, 1932.

The dog was studied as a potential reservoir for this typhus-like disease, apparently transmitted to man by the dog tick. In some instances experimental infection was induced, with a positive Weil-Felix reaction. Dogs showed little or no reaction, but successful transfer to man (fever therapy in dementia praecox) was accomplished by subcutaneous injection of dog's blood.

M. S. MARSHALL.

THE DESIGNATION "FIÈVRE BOUTONNEUSE." CHARLES NICOLLE, Arch. Inst. Pasteur de Tunis **21**:347, 1932.

"At different times, my lamented friend E. Conseil and I have been concerned with the employment of new and varied terms to designate the disease described for the first time by A. Conor and A. Bruch, in Tunis. I have demanded, moreover, that the term exanthematic fever should not be used to designate a particular disease, but the family of diseases of which the historic exanthematic typhus is the oldest and best known, 'button fever' being classed in this same family. The First Congress of Mediterranean Hygiene, meeting at Marseilles on Sept. 20 to 25, 1932, which counted among its members present most of those who in recent years have advanced our knowledge of 'button fever,' J. Pieri, Et. Burnet, Paul Durand, D. and J. Olmer, G. Blanc and J. Caminopetros, Plazy, Mercandier and Pirot, Pecori, Combiesco, etc., has adopted the following resolution:

"It [the Congress] is of the opinion that the denomination 'button fever' (*fièvre boutonneuse*), already employed, should be retained to designate the disease, described for the first time by Conor and Bruch in Tunis and discovered at various points around the Mediterranean basin, especially in Marseilles by Olmer, in Italy and in other countries. The term 'exanthematic fever' should be reserved for the group of diseases of which exanthematic typhus is the type and of which button fever is a part.

"Thus is definitively established the excellent term under which the Tunis doctors recorded, in 1910, this new disease of the group of exanthematic fevers."

APPENDICITIS AND ANGINA. L. ASCHOFF, Beitr. z. path. Anat. u. z. allg. Path. **87**:481, 1931.

Aschoff studied the relation of angina to acute appendicitis by bacteriologic investigation of the bacteria responsible for each condition. In about 70 per cent of cases of acute appendicitis the etiologic organisms are the anhemolytic streptococci Enterococcus A and B. In angina the predominating organism was found to be a hemolyzing streptococcus (60 per cent). Common to both was the presence in a small percentage of cases of the pneumococcus. Aschoff emphasizes that for each site the foregoing organisms are normal inhabitants, and that an inflammatory attack is due to a local increase in virulence. A sequential relation between angina and appendicitis in view of the disparity of the bacteriology is denied.

W. S. BOIKAN.

CONGENITAL TUBERCULOSIS OF THE LUNG DUE TO ASPIRATION OF AMNIOTIC FLUID. M. SIEGEL, Beitr. z. path. Anat. u. z. allg. Path. **90**:503, 1932.

A premature infant, whose mother died of pulmonary tuberculosis two days after the birth of the child, died at the age of 19 days. Symptoms of pneumonia developed four days before death. Both lungs were the seat of a widespread tuberculous bronchiolitis and caseous pneumonia. The process is considered a primary lesion that resulted from the aspiration of amniotic fluid containing tubercle bacilli.

O. T. SCHULTZ.

EXPERIMENTAL TUBERCULOSIS OF THE PANCREAS. A. VON VERES, Beitr. z. path. Anat. u. z. allg. Path. **90**:673, 1933.

The reported rarity of tuberculous involvement of the pancreas in generalized human tuberculosis led to the experiments here reported. Intraperitoneal, subcutaneous or direct intrapancreatic inoculation of guinea-pigs was followed by tuberculosis of the pancreas. The author concludes that pancreatic tissue offers no especial resistance to tuberculous infection and that more careful histologic examination of the pancreas in human tuberculosis would reveal a greater frequency of involvement of this organ than has been reported.

O. T. SCHULTZ.

THE CULTIVATION OF THE VIRUS OF INGUINAL LYMPHOGRANULOMA. KURT MEYER and H. E. ANDERS, Klin. Wchnschr. **11**:318, 1932.

Cultures were prepared from human lymphogranuloma exudate, the procedure of Maitland being used, and the virus was propagated in passage. The liquid culture was injected into guinea-pigs in the inguinal region. In half of the animals, changes occurred in the inguinal glands and in one instance in an associated iliac gland which corresponded to the changes in human glands. If identification of an infectious disease is acceptable by means of histologic methods, then the cultivation and propagation of the virus of lymphogranuloma of the inguinal glands appears possible.

DAVID O. ROSBASH.

DETECTION OF TUBERCLE BACILLI IN CIRCULATING BLOOD. A. AXEN, Klin. Wchnschr. **11**:1949, 1932.

No tubercle bacilli could be isolated from the blood of diseased guinea-pigs or human beings, or from tonsillar tissue. The discrepancies between the results of this experiment and those obtained by Löwenstein could not be attributed to differences in technic or in the culture medium employed.

D. O. ROSBASH.

BACILLEMIA AND BACILLURIA IN TUBERCULOSIS. H. DEIST, Klin. Wchnschr. **12**:26, 1933.

From 287 patients, including 213 women with all forms and stages of tuberculosis, 18 children with different localizations of the disease, 36 mature patients

with extrapulmonary tuberculosis, and 30 nontuberculous patients, the author obtained 4 positive cultures from the blood of 3 patients with tuberculosis, employing Löwenstein's method. Culturing urine daily for twenty-five days from 31 patients having neither vesical nor renal tuberculosis resulted in 12 positive and 19 negative results.

D. O. Rosbash.

Hematogenous Infection of the Tonsils. C. Krauspe, Virchows Arch. f. path. Anat. **287**:139, 1932.

Previously reported results of experimental work had led the author to conclude that the tonsils may be involved by way of the blood stream and that the resulting involvement is often not to be readily distinguished from such as occurs by way of the exposed surface of the tonsil. The present communication is based on the histologic examination, in serial sections, of the tonsils of eleven children and fourteen adults who died of a variety of acute infectious diseases. The tonsils of twenty-five children whose death was not due to acute infection were also examined, but somewhat less thoroughly. In most of the cases of infection, especially in children, the tonsils revealed inflammatory reactions that the author interprets as the result of hematogenous localization. The earliest stages were noted in and about the arterioles of the follicles and in the subepithelial capillaries. Necrosis and abscesses were frequently observed. The bacteria could usually be demonstrated in the lesions. Streptococci were the most important invading organisms in children. In both children and adults, localization of bacteria in the subepithelial capillaries led to inflammatory foci not to be distinguished from primary crypt infections. Involvement of the tonsils was seen in one case of typhoid and one of bacterial glomerulonephritis.

O. T. Schultz.

Value of Animal Inoculation in the Diagnosis of Undulant Fever. H. Lotze, Virchows Arch. f. path. Anat. **287**:162, 1932.

As an aid in the diagnosis of infections by Bacillus abortus, Lotze strongly recommends animal inoculation. For each inoculation he uses two full-grown guinea-pigs, one male and one female. The nonagglutination of the organism by the blood of the animals should be determined prior to their use. The material to be inoculated is injected subcutaneously at the bedside of the patient. The character of the material used is not stated; presumably it is blood. The diagnosis may be established within from three to seven days after inoculation by performing an agglutination test with blood withdrawn from the inoculated animals by heart puncture. The temperature curve of the animals is diagnostic at the latest by the fourth week after inoculation. The diagnosis may be further established in the fifth week by the macroscopic lesions of the inoculated animals.

O. T. Schultz.

Paralytic Dementia as a Spirochetosis. W. K. Nelezky, Virchows Arch. f. path. Anat. **288**:346, 1933.

The brains of twenty unselected and untreated persons with progressive paralysis were subjected to microscopic study with special reference to the presence of spirochetes and to the numerical relationship of the latter to the clinical course of the disease. The organisms were demonstrated in fifteen (75 per cent) of the brains. Exclusion of brains with arteriosclerotic softening and of the brains of those who died of acute infection with high fever increased the positive percentage to 100. The number of typical and degenerated spirochetes bore a direct relation to fatal seizures and to the duration between the latter and the time of death. The seizures of paralysis are the result of periodic increase in the number of spirochetes in the cerebral cortex. During such periods of increased multiplication, the organisms may appear in the circulating blood. Death due to marasmus may be preceded by an increase in the number of organisms without any definite change in the characteristic symptoms of the

disease. When death followed a seizure, many of the spirochetes were partly lysed and many had been phagocytosed. Lysis predominated over phagocytosis. The latter process was by the cells of the mesoglia, which the author considers a part of the reticulo-endothelial system. O. T. SCHULTZ.

PHAGOCYTIC ACTIVITY OF CAPILLARY ENDOTHELIUM. W. KLOSTERMEYER, Virchows Arch. f. path. Anat. **288**:703, 1933.

Although some observers have ascribed to ordinary capillary endothelium the capacity for vital storage, the weight of opinion would limit this phenomenon to the reticulo-endothelium in the narrower sense. The difference in the phagocytic activity of the two kinds of endothelium may be due to differences in surface tension or in electric charge. To investigate the latter possibility, the electric charge of bacteria was altered. But when such bacteria were injected into mice they were not more readily taken up by the capillary endothelium of the lung than were untreated bacteria. If the animals were sensitized with either a specific or a nonspecific antigen, the capillary endothelium of the lungs took up bacteria as readily as did the reticulo-endothelial system. O. T. SCHULTZ.

PURULENT MENINGITIS DUE TO BACILLUS ENTERITIDIS. P. RIEPER, Virchows Arch. f. path. Anat. **289**:301, 1933.

Meningeal symptoms developed in a 3½ month old nursling seven days before death. Bacillus enteritidis was grown in pure culture from the spinal fluid during life. The total duration of the illness was twenty-six days; it began with a furuncle of the buttock, which was followed by furuncles on other parts of the body. Five previously reported cases of meningitis due to B. enteritidis are summarized; all occurred in young nurslings. O. T. SCHULTZ.

AN UNUSUAL BACTERIUM IN ABSCESSES OF THE BRAIN. WILLY BENDER, Zentralbl. f. Bakt. (Abt. 1) **122**:469, 1931.

Four patients with abscesses of the brain revealed an unusual type of bacterium as the causative agent. The micro-organism was found in pure culture either in the cerebrospinal fluid or in the abscesses, showed marked variations from coccus to rod forms, did not ferment the usual sugars and was gram-negative and non-motile. The author suggests the name Bacterium alternans.
PAUL R. CANNON.

THE FATE OF PARENTERALLY INTRODUCED BACTERIOPHAGE IN THE BODY. P. SMIRNOW and M. GOLDIN, Zentralbl. f. Bakt. (Abt. 1) **122**:512, 1931.

Bacteriophage against the dysentery bacilli of Shiga and of Flexner was injected subcutaneously or into the testes of guinea-pigs and its presence in the various organs determined. It disappeared from the blood, liver, kidneys, lungs, brain, testes and intestine within from one to three days following subcutaneous injection, but persisted in the lymph nodes and spleen for from thirteen to seventeen days. When injected directly into the testes it persisted there for two weeks. When the bacteriophage, however, was injected subcutaneously into guinea-pigs previously immunized against it, it could be recovered within twenty-four hours only from the liver, spleen and lymph nodes and had disappeared from these organs at the end of forty-eight hours. PAUL R. CANNON.

Immunology

THE RESPIRATION OF PHAGOCYTOSIS. C. W. BALDRIDGE and R. W. GERARD, Am. J. Physiol. **103**:235, 1933.

By means of the Warburg manometer, the respiration of leukocytes during phagocytosis was studied. A constant increase in oxygen consumption was observed

during this activity, the rise beginning at once, reaching a maximum value of about twice that of the inactive state in about fifteen minutes and ending in from ninety to one hundred and fifty minutes. The main burst of extra respiration lasted from ten to fifteen minutes, after which the maintained level was relatively little above the control value. The authors believe that this phase may represent the liberation of extra energy in digestion, the earlier and greater rise being that of engulfment.

H. E. EGGERS.

AN UNUSUAL BLOOD GROUP. M. M. WILHELM and E. E. OSGOOD, Arch. Int. Med. **52**:133, 1933.

A subgroup (B_1) of group B is described which is characterized by a serum that agglutinates 33 per cent of group B cells and 47 per cent of group O cells and by cells which are agglutinated by 43 per cent of group B serums. From absorption experiments the characteristics of this serum may be explained by the presence of a single extra agglutinin in the group B_1 serum and of a corresponding single agglutinogen occurring in some of the cells in each of the three groups (A, B and O) tested. Previously reported subgroups are summarized in a table. Precautions necessary to prevent accidents are outlined.

AUTHORS' SUMMARY.

ANTIPOLIOMYELITIC SERUM FROM MONKEYS. FREDERICK EBERSON, J. Immunol. **24**:433, 1933.

Macacus rhesus monkeys were apparently immunized against the virus of poliomyelitis by a series of subcutaneous injections of a culture of an organism cultivated from Berkefeld N filtrates of poliomyelitis virus. The protection conferred was measured by the neutralizing power of their serums for poliomyelitis virus. In two instances the resistance of the monkeys to intracerebral injection of the virus was also tested. The serums neutralized the poliomyelitis virus in vitro completely or in part. The two intracerebral inoculations showed that the monkeys had become resistant to infection by this route. During the course of immunization with the living cultures one animal contracted typical poliomyelitis. In an earlier series of experiments three monkeys showed symptoms and signs of typical abortive infection. The cultures used were in the twenty-fourth subplanting and represented a dilution of the original virus material of approximately 2×10^{-38}. The results are discussed with reference to a possible survival of any hypothetical adsorbed virus and with reference to the viability of the virus as compared with the cultures at incubator temperature. The experiments, it is believed, confirm further the previously reported observations (*J. Lab. & Clin. Med.* **18**:565, 1933) on the possible relationship of this organism to the poliomyelitis virus.

AUTHOR'S SUMMARY.

AGGLUTINATION IN VARICELLA. C. RUSSELL AMIES, Lancet **1**:1015, 1933.

The findings of Aragao and of Paschen that elementary bodies are present in the fluid of the vesicles of varicella have been amply confirmed. A method of preparing purified suspensions of these bodies is described. Such suspensions are specifically agglutinated by the serum of patients convalescent from varicella. The results obtained in a series of sixty-one agglutination tests are recorded. The constant presence of the elementary bodies in the fluid of the early vesicles and the fact that they are specifically agglutinated by the homologous antiserum are regarded as strong evidence in favor of the view that these represent the infecting agents of varicella.

AUTHOR'S SUMMARY.

SPECIFIC LESIONS OF THE KIDNEY AND LIVER INDUCED BY CYTOTOXIC SERUMS. M. MASUGI, Beitr. z. path. Anat. u. z. allg. Path. **91**:82, 1933.

For his experimental investigation Masugi used the rat, whose small size makes it possible to use relatively large doses of antiserum. He ascribes the

negative and contradictory findings of the many investigators who have preceded him in this field to the fact that insufficiently large doses of serum were used when rabbits and dogs were employed as the experimental animals. The nephrotoxic and hepatotoxic antiserums were prepared in the rabbit, and a relatively high degree of organ specificity was obtained. In the kidney the primary damage produced by the nephrotoxic antiserum was to the glomerular capillaries and the afferent arterioles. In the liver the hepatotoxic antiserum manifested its primary effects on the vessels of the peripheral zone of the lobule, the small vessels of the interlobular tissue and the small branches of the hepatic artery. The vascular reaction was similar to that recently described by a number of observers in local hyperergic inflammation. The parenchymatous alterations are secondary to the changes in the vessels. The resulting lesions are like those of the kidney in human glomerulonephritis and those of the liver in eclampsia, from which the author concludes that allergy, or antibody-antigen reaction in its wide sense, is the underlying factor in the pathogenesis of these two human diseases.

O. T. SCHULTZ.

POSTMORTEM CHANGES IN THE SPINAL FLUID. S. SÜMEGI, Frankfurt. Ztschr. f. Path. **44**:283, 1932.

Normal antibodies appeared in the cerebrospinal fluid about twenty-four hours after death. At first complement alone could be demonstrated, but later, about thirty-four hours after death, normal hemolysin was also present. The appearance of the normal antibodies is correlated with the increase in the amount of protein in the cerebrospinal fluid after death and also with the shift to the left of the precipitation zone of the colloid curves.

AUTHOR'S SUMMARY.

REACTIONS OF TISSUE IN EXPERIMENTALLY SENSITIZED RABBITS. K. APITZ, Virchows Arch. f. path. Anat. **289**:46, 1933.

A series of twenty-four rabbits was sensitized with horse serum. At various intervals after sensitization the rabbits received a subcutaneous injection of the antigen, and notations were made of the resulting local Arthus reaction. The animals then received a massive intravenous dose of the antigen. Seven died of acute shock, five more died after prolonged symptoms of shock, and twelve recovered and were killed at varying periods. The heart, liver, spleen and blood vessels were subjected to histologic study. The reactions described are in part degenerative and in part inflammatory. The degenerative reactions consisted of focal albuminoid degeneration and necrosis, followed by the deposition of calcium, which was noted especially in the liver and heart. Inflammatory proliferative and lymphocytic infiltrative reactions were noted, especially in the myocardium of the right side of the heart and in the blood vessels. Further mesenchymal reactions were large cell transformation of the spleen and the development of monocytic and myeloid cells in the liver. The development of the changes described is influenced by nonspecific factors. Whether the mesenchymal changes are to be interpreted as a defense reaction the author was not able to determine from his experiments.

O. T. SCHULTZ.

LYSIS OF TUBERCLE BACILLI IN SENSITIZED RESISTANT SPECIES OF ANIMALS. PHILIPP SPANIER, Zentralbl. f. Bakt. (Abt. 1) **121**:451, 1931.

The author maintains that the leukocytes of animals which are resistant to tuberculosis (the dog, horse and rat), when mixed with tubercle bacilli and kept for five days at 37 C., cause more granular degeneration of the bacilli than do the leukocytes of susceptible animals (the guinea-pig, the rabbit and man). He assumes, therefore, that the leukocytes of the resistant animals contain more tuberculolytic substance and are better prepared to liberate undenatured antigen from the tubercle bacilli. Dogs were infected intraperitoneally with a bovine strain of a virulent tubercle bacillus and were reinfected subcutaneously in a sterile abscess produced

by the injection of oil of turpentine with from 50 to 100 mg. of living tubercle bacilli. Acid-fast stains, made twenty-four hours later, showed many granular forms of tubercle bacilli in the pus from the abscess. Cultures of this material were negative, and guinea-pigs which received injections of it remained healthy. Similar material from the abscess was diluted with a sterile salt solution and placed in sterile flasks, at 37 C., and 50 mg. of living tubercle bacilli was placed in it. After one week the tubercle bacilli contained many granules, and many were no longer acid-fast. After from two to two and one-half months, cultures of this material were sterile. Observations on pus from the abscesses of normal control dogs showed a persistence of tubercle bacilli in the mixture. The injection of the autolysate from the previously infected dogs into tuberculous guinea-pigs caused a general tuberculin reaction. Similar material, autolyzed for two months, when injected into rabbits and guinea-pigs, caused no tuberculosis. The possibilities of using such autolysates in immunization are being studied and will be reported on later.

PAUL R. CANNON.

THE SHWARTZMAN PHENOMENON. H. GROSS, Zentralbl. f. Bakt. (Abt. 1) **122**: 96, 1931.

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PAUL R. CANNON.

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Portions of skin from rabbits highly immunized against paratyphoid-enteritis micro-organisms were transplanted into normal rabbits whose blood serums contained no agglutinins before the transplantation. Agglutinins soon appeared in the serum of the latter rabbits, the maximum titer being reached on the twelfth day. If the transplanted skin was injured by the induction of necrosis, the agglutinin titer of the blood serum dropped promptly, and if comparable amounts of skin from highly immunized rabbits were macerated and injected subcutaneously into normal rabbits, only traces of agglutinin appeared in the blood serum. The author concludes that the agglutinins are not transferred passively in the transplantations of skin, but that they are produced locally in the skin of the rabbit because of the large amount of histiocytic tissue in the skin.

PAUL R. CANNON.

RELATION BETWEEN AN ACID OR AN ALKALINE DIET AND IMMUNITY: A. M. BONANNO, Ztschr. f. Immunitätsforsch. u. exper. Therap. **77**:19, 1932.

The acid-base equilibrium of rabbits and guinea-pigs was changed by feeding them with calcium and ammonium chloride, with sodium bicarbonate and with sodium citrate. An acid diet was followed by a decrease in the bactericidal and complementary qualities of the blood. A change in the normal albumin-globulin ratio in the blood was noted, there being a rise in albumin and a drop in globulin. An alkaline diet was without effect. An acid diet impaired the ability to produce immune agglutinins and to resist infection and increased the severity of anaphylactic reactions. A modification of the diet in either acid or alkaline reactions led to a marked lowering of resistance to intraperitoneal infection with tubercle bacilli.

I. DAVIDSOHN.

negative and contradictory findings of the many investigators who have preceded him in this field to the fact that insufficiently large doses of serum were used when rabbits and dogs were employed as the experimental animals. The nephrotoxic and hepatotoxic antiserums were prepared in the rabbit, and a relatively high degree of organ specificity was obtained. In the kidney the primary damage produced by the nephrotoxic antiserum was to the glomerular capillaries and the afferent arterioles. In the liver the hepatotoxic antiserum manifested its primary effects on the vessels of the peripheral zone of the lobule, the small vessels of the interlobular tissue and the small branches of the hepatic artery. The vascular reaction was similar to that recently described by a number of observers in local hyperergic inflammation. The parenchymatous alterations are secondary to the changes in the vessels. The resulting lesions are like those of the kidney in human glomerulonephritis and those of the liver in eclampsia, from which the author concludes that allergy, or antibody-antigen reaction in its wide sense, is the underlying factor in the pathogenesis of these two human diseases.

O. T. SCHULTZ.

POSTMORTEM CHANGES IN THE SPINAL FLUID. S. SÜMEGI, Frankfurt. Ztschr. f. Path. **44**:283, 1932.

Normal antibodies appeared in the cerebrospinal fluid about twenty-four hours after death. At first complement alone could be demonstrated, but later, about thirty-four hours after death, normal hemolysin was also present. The appearance of the normal antibodies is correlated with the increase in the amount of protein in the cerebrospinal fluid after death and also with the shift to the left of the precipitation zone of the colloid curves.

AUTHOR'S SUMMARY.

REACTIONS OF TISSUE IN EXPERIMENTALLY SENSITIZED RABBITS. K. APITZ, Virchows Arch. f. path. Anat. **289**:46, 1933.

A series of twenty-four rabbits was sensitized with horse serum. At various intervals after sensitization the rabbits received a subcutaneous injection of the antigen, and notations were made of the resulting local Arthus reaction. The animals then received a massive intravenous dose of the antigen. Seven died of acute shock, five more died after prolonged symptoms of shock, and twelve recovered and were killed at varying periods. The heart, liver, spleen and blood vessels were subjected to histologic study. The reactions described are in part degenerative and in part inflammatory. The degenerative reactions consisted of focal albuminoid degeneration and necrosis, followed by the deposition of calcium, which was noted especially in the liver and heart. Inflammatory proliferative and lymphocytic infiltrative reactions were noted, especially in the myocardium of the right side of the heart and in the blood vessels. Further mesenchymal reactions were large cell transformation of the spleen and the development of monocytic and myeloid cells in the liver. The development of the changes described is influenced by nonspecific factors. Whether the mesenchymal changes are to be interpreted as a defense reaction the author was not able to determine from his experiments.

O. T. SCHULTZ.

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I. DAVIDSOHN.

APPLICATION OF RECENT PRECIPITATION REACTIONS FOR THE DEMONSTRATION OF SYPHILIS IN RABBITS. F. E. HAAG and W. LEVEN, Ztschr. f. Immunitätsforsch. u. exper. Therap. **77**:25, 1932.

The Kahn test gave uniformly negative results with diluted serums (1:10) of normal healthy rabbits. The reactions were positive in a considerable number of cases when undiluted serum was used or when the Kahn citochol or the Meinicke test was employed. Latent syphilis could not be detected by means of any of these tests. In the presence of an active infection the Kahn citochol test was the only one that produced a considerable number of positive reactions, but in view of the positive results in healthy rabbits no definite conclusions could be drawn. No differences were observed between the serum reactions of animals infected with syphilis and those of rabbits infected with frambesia tropica. The results contradict the report of Taishin Saito (*Ztschr. f. Hyg. u. Infektionskr.* **110**:603, 1929), who claimed to have found in the Kahn test with diluted serum a means of diagnosing syphilis in the rabbit. The Kahn citochol reaction and particularly the second modification of the Mueller *"Ballung"* reaction were found very well suited to the diagnosis of syphilis in rabbits, but only after precipitation of globulins in the serum with diluted hydrochloric acid by the method of Sachs and Georgi. Triple and double dilutions had to be employed instead of the original tenfold dilution.

I. DAVIDSOHN.

SEROLOGIC SPECIFICITY OF PLACENTAL TISSUE. G. F. DE GAETANI, Ztschr. f. Immunitätsforsch. u. exper. Therap. **77**:43, 1932.

Serums of rabbits immunized with an aqueous suspension of human placental tissue reacted with placental extracts and with human red blood cells. The material used for immunization was not free from red blood cells. No attention was paid to the blood group of the persons whose placentas were employed. Some organ specificity was present, as demonstrated by proper absorption experiments. A few of the serums also reacted with the placenta of the ox. From the fact that the albumin fraction of the antiserums was shown to contain the bulk of the antibodies, Gaetani concludes that the antibodies in the serum were of the Forssman type, but he admits that their source is probably in the red blood cells not removed from the placental tissue. No reaction took place with boiled placental tissue. Immune serums obtained with boiled placental tissue contained species-specific lipoid antibodies.

I. DAVIDSOHN.

ORAL IMMUNIZATION WITH VIRULENT STAPHYLOCOCCI AND STREPTOCOCCI. HANS WINZELER, Ztschr. f. Immunitätsforsch. u. exper. Therap. **77**:60, 1932.

Guinea-pigs weighing from 230 to 280 Gm. were fed living or killed cultures of highly virulent strains of Staphylococcus aureus or Streptococcus haemolyticus. Some of the animals were treated with ox bile, a sodium salt of a bile acid or sodium benzoate previous to being given the bacterial suspension. When living bacteria were used, active immunity against subsequent parenteral injections of multiple lethal doses of Staph. aureus was obtained in seventeen of twenty-five animals. Dead bacteria only slightly increased the natural resistance. The immunization with streptococci was not successful. The preliminary administration of bile or bile salts was not found necessary.

I. DAVIDSOHN.

SEROLOGIC ANALYSIS OF EGG WHITE. M. SHARMA, Ztschr. f. Immunitätsforsch. u. exper. Therap. **77**:79, 1932.

Immune serums produced in rabbits with boiled egg white reacted best in complement-fixation tests with the homologous antigen heated to 100 and to 80 C.; the fixation was either insignificant or absent with egg white heated to below 70 C. If the quantity of the antibody was increased, complement was fixed even with the raw antigen. A similar specificity prevailed in the immune serums produced

with raw egg white, which did not react with antigen heated above 80 C. Egg white heated at 70 C. occupied a middle position, being able, more than any other, to produce antiserum which under proper conditions reacted both with unheated and with boiled antigens, though here also the optimum fixation occurred with the homologous antigen. The absorption of complement-fixing antibodies in an immune serum obtained with boiled egg white was also best with the homologous antigen. Extracts of egg white prepared with 50 per cent alcohol fixed complement with some boiled egg white antiserums; other alcoholic extracts failed to react.

I. DAVIDSOHN.

Tumors

EXPERIMENTAL EPITHELIAL GROWTHS IN THE LUNG AFTER INSUFFLATION OF TAR. L. M. SCHABAD, Ztschr. f. Krebsforsch. **38**:154, 1932.

Schabad studied the effects of a single intratracheal insufflation of coal tar on the lungs of guinea-pigs, the animals being kept under observation up to fourteen months. There was an epithelial overgrowth of adenomatous type, with a stroma of inflammatory connective tissue; the growth could be differentiated from adenoma by the lack of elastic tissue in the stroma. In regard to the sources of the epithelium, the author concludes that, in part, it is of bronchial origin; but the occurrence of similar lesions in the extreme periphery of the lung, far from direct bronchial communication, leads him to the belief that in part it may come from the alveolar linings, contrary to the usually accepted current view that these are not of epithelial character. He infers, with apparent justice, that some of the alleged experimental cancers of this organ reported after the use of tar are really the type of lesion he obtained. In these growths, there was no ground for assuming a malignant character; they never penetrated the pleura, nor were metastases ever observed. Indeed, Schabad feels called on to explain why cancer did not occur; he lays little stress on the fact that guinea-pigs are notoriously immune to the cancerigenic action of tar, and states that in his belief this property is lost soon after application to tissue, and that thereafter tar behaves as a relatively inert oil, so that repeated applications are necessary to exert a cancerigenic effect.

H. E. EGGERS.

PHOSPHATASE IN TUMORS. S. EDLBACHER and WALDEMAR KUTSCHER, Ztschr. f. physiol. Chem. **207**:1, 1932.

The activity of the nucleotidase in the liver and in tumors can be increased through acetone extraction of the tissues. The acetone extract contains an inhibitor of the nucleotidase. Cysteine, glutathione and hydrocyanic acid, as well as copper ions, inhibit the nucleotidase. The natural inhibitor is possibly identical with glutathione. The activation of nucleotidase in minced liver by hydrocyanic acid is explained by the high heavy metal content of this organ. It is suggested that the nucleotidase and arginase are heavy metal ferments. While the tumor hexophosphatase is as strongly inhibited by cysteine, glutathione and hydrocyanic acid as the nucleotidase, the liver hexophosphatase is only half as much inhibited by hydrocyanic acid as the nucleotidase and is only weakly or is not inhibited by cysteine and glutathione.

WILHELM C. HUEPER.

HEREDITARY NEUROFIBROMA AND DIFFUSE MENINGEAL GLIOMATOSIS. F. HARBITZ, Norsk mag. f. lægevidensk. **93**:841, 1932.

In a case of neurofibroma and diffuse meningeal gliomatosis in a boy who died at the age of 9, Harbitz saw a threefold interest. The hereditary basis was marked; the child was the sixth of a family of nine children, of whom the five oldest had multiple neurofibromas. Recklinghausen's disease in the mother, then 19, was described by Harbitz in 1908. In addition to the peripheral neurofibroma, the patient had gliomatosis in the central nervous system, with the starting point

probably in the cauda equina, and these two tumors are regarded as an outcome of the same constitutional factor, the case thus connecting neurofibroma in the peripheral nerves with gliomatosis in the central nervous system. The diffuse extent of the masses in the leptomeninges of the spinal cord and the brain was so pronounced that the cord and medulla seemed to be cast in tumors.

Medicolegal Pathology

DEMONSTRATION OF CARBON MONOXIDE IN THE EXHUMED CADAVER. STANISLAW LAGUNA, Deutsche Ztschr. f. d. ges. gerichtl. Med. **21**:512, 1933.

Reports in the literature indicate that carbon monoxide has been successfully demonstrated in the disinterred cadaver from fourteen to one hundred and twenty-two days after death. The author had occasion to exhume a body two hundred and ten days after death. In spite of the fact that the tissues were putrefying, a definite bright pink color was noted in the muscles, in some of the organs and in the pleural and peritoneal transudates. Spectroscopic examination of these transudates demonstrated the absorption band for carbon monoxide hemoglobin.

JACOB KLEIN.

TRAUMATIC INTRAPERITONEAL RUPTURE OF THE URINARY BLADDER. STANISLAW LAGUNA, Deutsche Ztschr. f. d. ges. gerichtl. Med. **22**:14, 1933.

A drunken woman, hospitalized on suspicion of poisoning, died four days after admission. At autopsy the abdominal cavity contained 2,500 cc. of a clear, straw-colored fluid. The peritoneum was hyperemic and covered with a fibrinopurulent exudate, particularly on the wall of the bladder, which showed a midline tear 5 cm. long. The history indicated that the patient had fallen while dancing and that her partner had accidentally stepped on the lower part of her abdomen.

JACOB KLEIN.

FLUORIDE POISONING. M. FLAMM, Deutsche Ztschr. f. d. ges. gerichtl. Med. **22**:21, 1933.

A 22 year old workman in a brewery accidentally swallowed some 30 per cent hydrofluosilicic acid used as a disinfectant and was immediately seized with cramps, vomiting and diarrhea. He died four days later, after the development of convulsions, cyanosis and stupor. At autopsy there were destruction of the epithelium in the pharynx and esophagus, congestion of the larynx and trachea, marked edema of the lungs, bleeding and necrosis of the gastric mucosa, inflammation and punctate hemorrhages in the jejunum, acute toxic hemorrhagic nephritis and cerebral hyperemia and edema. The use of fluorides should be restricted and more strictly supervised.

JACOB KLEIN.

GROUP SPECIFICITY OF SPERMATOZOA. A. SCHMIDT and H. ECK, Deutsche Ztschr. f. d. ges. gerichtl. Med. **22**:43, 1933.

By means of agglutinin absorption tests it is possible to determine the blood group from spots of semen on linen, even after from two to three years. The spermatozoa belong to the same blood group as the person's blood. This is of practical medicolegal significance.

JACOB KLEIN.

SUBGROUPS A_1 AND A_2 IN INVESTIGATIONS OF PATERNITY. ERIK WOLFF and BENGT JONSSON, Deutsche Ztschr. f. d. ges. gerichtl. Med. **22**:65, 1933.

A determination of subgroups A_1 and A_2 is readily made by the glass slide test with a standard 1 per cent erythrocyte suspension, the readings being both macroscopic and microscopic. In children A_2 cannot be determined before the

age of 6 months. Studies in 883 cases of doubtful paternity confirm the four gene hypothesis of blood group heredity. A table has been compiled which gives the blood groups of the mother and child and indicates the groups which eliminate a person as the possible father. Moreover, given a father with a certain blood group, that of the mother and child may be determined. The forensic importance of subgroups is emphasized, especially groups A_1 and A_2 and M N.

JACOB KLEIN.

SPONTANEOUS RUPTURE OF AN AORTA WITH MUCOID DEGENERATION OF THE MEDIA. FRITZ HELLNER, Deutsche Ztschr. f. d. ges. gerichtl. Med. **22**:86, 1933.

A 49 year old man collapsed while lifting a heavy barrel and died shortly afterward. There were hemopericardium, cardiac hypertrophy, dilatation of the ascending aorta and a tear in the posterior wall of the aorta above the posterior valve. Microscopically there were mucoid degeneration of the media and destruction of the elastica. The author discusses the various causes of spontaneous rupture of the aorta as described in the literature.

JACOB KLEIN.

TECHNIC OF DETERMINATION OF M AND N GROUPS IN BLOOD STAINS. A. LAUER, Deutsche Ztschr. f. d. ges. gerichtl. Med. **22**:86, 1933.

Landsteiner's technic based on the principle of absorption was used. The blood stain, washed out with distilled water, was mixed with a 2 per cent suspension of standard erythrocytes on glass slides which had been cleaned with a 10 per cent solution of liquid petrolatum in xylene. Using this technic, the authors were able to recognize M and N groups in forty specimens of dried blood from one week to three months old. The method was also successfully used in two medicolegal cases.

JACOB KLEIN.

DETERMINATION OF BLOOD GROUPS BY EXAMINATION OF HUMAN FECES. H. HODYO, Deutsche Ztschr. f. d. ges. gerichtl. Med. **22**:95, 1933.

Group-characteristic substances are found in body fluids, secretions and excretions. The author mixed from 10 to 20 Gm. of feces with twice as much physiologic solution of sodium chloride or distilled water and filtered the mixture through several layers of gauze. The filtrate was dried on a water bath at from 50 to 70 C. The resulting powder was tested by the absorption technic. Blood group characteristics were found in the normal stool which agreed with those shown by the control tests on the person's blood. Sometimes the reaction was distorted by the presence of hemolysins, agglutinins and inhibiting substances in the stool.

JACOB KLEIN.

DEATH DURING BATHING. FRITZ BERNSTEIN, München. med. Wchnschr. **79**: 1889, 1932.

Grassl has reported attacks of illness during bathing which may be attributed to cold allergy. This condition is manifested by urticaria, hemoglobinuria, asthma, collapse, lowering of the blood pressure, leukocytosis and, in particularly susceptible persons, unconsciousness. The reaction occurs usually from five to fifteen minutes after exposure to cold. Doubtless some cases of drowning are due to cold allergy in persons who have previously shown evidence of hypersensitiveness to cold. A simple test for determining the existence of such an idiosyncrasy is to place a piece of ice on the healthy skin for from one to two minutes; after from five to fifteen minutes a wheal forms in the susceptible person.

JACOB KLEIN.

DEATH DURING BATHING. S. J. THANNHAUSER, München. med. Wchnschr. **79**: 1890, 1932.

A 46 year old athletic physician noticed erythema and urticaria of the palms and soles after bathing in cold water. Wheals were noted on other parts of the body on exposure to cold water. After a shower there was redness of the entire body, followed by a greenish-white discoloration and a feeling of chilliness which disappeared after half an hour. While bathing in a mountain lake after vigorous exercise he observed erythema, pruritus and a feeling of oppression in the chest. He immediately left the water and sank into a chair. Although he was not unconscious, he was weak and unable to move. Vigorous colonic peristalsis soon developed; the skin was greenish, and the pulse was slow. There was a feeling of intense cold over the entire body. He recovered after one hour. In the evening, while eating, he experienced a sudden feeling of cold and loss of appetite, but there were no changes in the skin. This was relieved by drinking alcohol. Cold urticaria and resulting shock represent an exaggeration of the normal heat regulation; perhaps a histamine substance is liberated. Drowning may readily result from the adynamic reaction.

JACOB KLEIN.

BULLET EMBOLUS OF THE PULMONARY ARTERY. R. PALTAUF, Wien. klin. Wchnschr. **46**:602, 1933.

A 21 year old man was shot in the third intercostal space 3 cm. from the midline. Death occurred from hemopericardium seven days afterward. The track of the bullet led through the upper lobe of the left lung and the pericardium at the origin of the pulmonary artery, which showed no wound of exit. A 6.35 mm. steel jacket bullet was found in the branch of the pulmonary artery to the lower lobe of the right lung, where it had caused pressure necrosis with infarction of the lung. The pleuritis resulting from the infarct provoked coughing, which opened the wound in the pulmonary artery and caused death from hemopericardium. This is one of the few instances in which a bullet has been transported by the circulation.

Technical

STAINING OF OLIGODENDROGLIA AND OF MICROGLIA IN CELLOIDIN SECTIONS. ARTHUR WEIL and HAROLD A. DAVENPORT, Arch. Neurol. & Psychiat. **30**:175, 1933.

The authors give a modification of Stern's method of staining oligodendroglia and microglia in celloidin sections. For the staining of microglia, the sections are washed in distilled water, are put for ten or twenty seconds into an ammonia-silver nitrate solution, from which they are transferred to a solution of formaldehyde, and after three changes of water, are dehydrated and mounted in Canada balsam.

Practically the same method is used for staining oligodendroglia, with slight modifications, for which the original article should be consulted. The appended photomicrographs bring out well the advantages of the modified silver staining methods as given by Weil and Davenport.

GEORGE B. HASSIN.

IMPORTANCE OF ADEQUATE REDUCTION OF PEPTONE IN THE PREPARATION OF MEDIA FOR THE PNEUMOCOCCUS AND OTHER ORGANISMS. H. D. WRIGHT, J. Path. & Bact. **37**:257, 1933.

Difficulty in preparing broth suitable for the cultivation of pneumococci is largely due to incomplete reduction of peptone. This may readily be overcome by adding peptone to the broth before any heat is applied and so exposing it to the powerful reducing action of meat or meat infusion during the steaming process. Huntoon's method of preparing broth owes its advantages to the fact that it provides for adequate reduction of the peptone. Other features in this method, especially filtration through glass wool, have been found to be of minor importance.

The presence of oxidized peptone in broth renders it relatively unsuitable for the cultivation of many aerobes and for that of Clostridium tetani. This inhibitory effect must be taken into account in experiments relating to accessory factors in growth and the oxidation-reduction potential. AUTHOR'S SUMMARY.

STAINING OF THOROTRAST IN TISSUE SECTIONS. L. PRÜSENER, Beitr. z. path. Anat. u. z. allg. Path. **91**:439, 1933.

The Best carmine method for glycogen stains thorotrast in tissue sections. A staining time of from ten to fifteen minutes is necessary. A concentrated alcoholic solution of chromotrope 2 R, applied for from five to ten minutes, also stains thorotrast. A hematoxylin nuclear stain may be combined with either of these methods. O. T. SCHULTZ.

NEW METHODS OF PRECIPITATION AND "BALL" REACTIONS FOR THE DEMONSTRATION OF SYPHILIS. JULIUS KISS, Ztschr. f. Immunitätsforsch. u. exper. Therap. **77**:195, 1932.

Kiss published, in 1930, a book entitled: "The Technic and Theory of the Examination of the Serum for Syphilis." In the present article, he summarizes the results of his studies since the publication of the book. Kiss advocates the use of antigens of known chemical composition. He employs a mixture of lecithin and cephalin prepared from alcoholic and ether extracts of the heart. Cephalin is the more sensitive of the two substances. It reacts with unheated serum. Various modifications of the Kahn precipitation test and of the Mueller *Ballung* test are offered. In the former, a more stable solution of the antigen is produced by removal of the alcohol from the antigen-salt solution mixture. In the Mueller test, the modified antigen contains mainly cephalin, with some admixture of lecithin. Unheated serum and different concentrations of sodium chloride are among the innovations. The *Ballung* test is, according to Kiss, the most sensitive of all methods. However, he emphasizes the danger of relying on precipitation tests or on the *Ballung* test only, and advocates strongly their employment together with a complement-fixation test. I. DAVIDSOHN.

EXAMINATION OF EXTRACTS FOR THE WASSERMANN REACTION BY MEANS OF NEPHELOMETRY. J. ADAMSKI, Ztschr. f. Immunitätsforsch. u. exper. Therap. **77**:247, 1932.

The ability of varying quantities of the extracts and of their fractions to prevent the precipitation of cholesterol was estimated with the apparatus of Moll. The animal species from which the heart muscle was obtained and the method of preparation influenced the protective ability of the extract. By combining certain extracts, the protective effect could be improved. Adamski gained the impression that extracts from hearts of animals killed during the summer and fall had greater protective ability than the heart extracts of animals killed during the winter or early spring. Such dependence on the time of the year may have some relation to the feeding. I. DAVIDSOHN.

PRACTICAL VALUE OF THE NEW MODIFICATION OF THE CITOCHOL REACTION. L. S. SCHIRWINDT, Ztschr. f. Immunitätsforsch. u. exper. Therap. **77**:294, 1932.

The new modification of the citochol reaction was published by Sachs and Witebsky in 1931. The changes concern mainly the dilution of the antigenic extract, with a resulting marked increase of sensitiveness. Schirwindt made parallel tests on 1,219 serums, employing the old citochol reaction, the Wassermann reaction and the Kahn test along with the new modification. The last test gave 8.4 per cent more positive reactions for persons known to have syphilis, and 10.7 per cent

more for persons with latent syphilis. To overcome the possibility of nonspecific positive reactions, which were very scarce, the parallel employment of the old modification is suggested. The use of a 3 per cent dilution of sodium chloride and the shaking by hand, if a shaking apparatus is not available, are preferable to the other procedures, such as using lower dilutions of sodium chloride and leaving the test materials at room temperature for from four to six hours. In experimental syphilis of rabbits, the modification of the citochol reaction proved by far the most sensitive, the next in sensitiveness being the Kahn reaction. Schirwindt compares the new modification with the "presumptive procedure" of Kahn.

I. DAVIDSOHN.

COMPARISON OF EXTRACTS OF SACHS-WITEBSKY WITH OWN EXTRACTS FOR THE CITOCHOL REACTION. S. L. SCHIRWINDT and A. V. ALEXEJEVA, Ztschr. f. Immunitätsforsch. u. exper. Therap. **77**:353, 1932.

Extracts prepared by the authors proved as efficient as those procured from Sachs' laboratory. That is considered an advantage as it removes the necessity of depending on one laboratory. The citochol reaction with cerebrospinal fluid showed a distinct lack of sensitiveness, but the test appears to have been greatly improved in this respect by the new modification of the antigen.

I. DAVIDSOHN.

MODIFICATION OF THE REACTION OF TSIEN-YUNG-TSÜ WITH INACTIVATED SERUM FOR THE DIAGNOSIS OF SYPHILIS. S. L. SCHIRWINDT and M. B. FEDOROWA, Ztschr. f. Immunitätsforsch. u. exper. Therap. **77**:359, 1932.

Tsien-Yung-Tsü utilizes shaking instead of the primary incubation in his technic of the complement-fixation test. He recently published a modification of the test in which inactive serum is used, and fresh rabbit serum is employed as the bearer of antisheep hemolysin and of complement. Schirwindt and Fedorowa preserve rabbit serum with 1 per cent of boric acid. In a series of 1,002 comparative tests, they found the modified method more sensitive than the Wassermann, the Kahn and the citochol reactions. They have not encountered nonspecific positive reactions.

I. DAVIDSOHN.

Society Transactions

CHICAGO PATHOLOGICAL SOCIETY

Regular Monthly Meeting, Nov. 13, 1933

E. H. HATTON, *President, in the Chair*

A RARE DENTAL ANOMALY ("DENS IN DENTE"). RUDOLF KRONFELD.

The dental anomaly usually described as *dens in dente*, or tooth inclusion, clinically appears as an enlarged or malformed anterior tooth the pulp chamber of which contains a small toothlike structure. This condition seems to be rare. Only about twelve cases have been reported in the literature. Most of these were said to be a twin formation whereby one tooth (parasite) developed within another (autosite). The arrangement of the hard tissues—enamel and dentin—in the inner tooth is inverse to that of the outer tooth. Thus the enamel of the outer tooth is on the outside and the dentin is on the inside, while the enamel of the inner tooth is inside of the dentin. By serial histologic sections through a tooth with this anomaly, it was possible to demonstrate that it is not a twin formation but a malformation of the germ of only one tooth, namely an invagination of one portion of the developing crown into the other. This explains not only the inverse arrangement of enamel and dentin in the inner invaginated portion but also the connective tissue and bone occasionally found in the central cavity within the *dens in dente*. The bone inclusion is periodontal in origin and has become pinched off and included in the center of the invaginated portion of the crown.

DISCUSSION

E. F. HIRSCH: The anomalous structure suggests the possibility of a fusion of two incisor-like teeth in mirror-image juxtaposition in which the structures of the root on the approximated surfaces either failed to develop or disappeared, while those of the crown persisted and fused.

INFECTIOUS CIRRHOSIS: REPORT OF A CASE. JAMES D. STEWART.

A white woman, aged 39, was well until three and a half years prior to death, when generalized pruritus was noted. This soon was complicated by attacks of icterus, gray stools, dark urine, moderate loss of weight and a tendency to bleed easily, but there was no pain or gastro-intestinal symptoms. These symptoms persisted through her illness. The first examination, fifteen months after the onset, disclosed an icteric, nervous person with a blood pressure of 110 systolic and 74 diastolic and a pulse rate of 72. The liver was enlarged and palpable on deep inspiration. Roentgen examinations revealed a normal stomach and duodenum, nonvisualization of the gallbladder and no stones. The results of the usual laboratory examinations were not significant except for an absence of free acid in the gastric contents after Ewald, histamine and alcohol meals. An exploratory operation disclosed nothing abnormal except enlarged and fibrosed periportal nodes. The condition persisted for two more years and became progressively worse. The liver gradually enlarged, and the spleen became palpable. No ascites developed. Hepatic function was adequate until a few months before death. An examination of excised skin eliminated hemochromatosis. When the patient entered the Billings

Hospital for the last time one month before her death she presented marked jaundice, a prolonged coagulation time, impaired hepatic function, anemia, a reticulocyte count of 6 per cent and the usual fragility of the red cells. Bile was obtained by duodenal tube. A cholecystoduodenostomy was performed and no further changes were noted. The patient's condition was satisfactory for three days, then a hemorrhage into the wound occurred, and her condition became progressively worse. Death followed ten days after the operation.

Necropsy disclosed an enlarged liver and spleen, no ascites, mild localized fibrinous and hemorrhagic peritonitis, a functional cholecystoduodenostomy, enlarged periportal lymph nodes, a patent biliary tract, a slightly dilated thin-walled gallbladder with a few small calcium carbonate and pigment concretions, bilateral hematomas of the ovary, a hematoma of the upper pole of the right kidney, absence of the right suprarenal gland, slight chronic fibrous mitral endocarditis and edema of the lower lobes of the lungs. The liver weighed 3,150 Gm. and was finely nodular. It showed slightly increased resistance and had a deep yellowish-green, firm, glistening parenchyma with a uniformly accentuated, translucent stroma. The spleen had a dark red pulp and weighed 700 Gm. The kidneys were jaundiced and large. The gastro-intestinal tract revealed no changes.

Histologically the liver had an increased perilobular and peripheral intralobular stroma. There were dense infiltrations of the portal areas by small round cells, mononuclear leukocytes and a few polymorphonuclear leukocytes and macrophages. The biliary epithelium was destroyed, and there were accumulations of bile pigment in small bile ducts and adjacent lobules. Stains and microchemical tests failed to demonstrate bacteria or iron.

The prolonged icterus, the large liver and spleen, the absence of ascites, the clay stools, the inflammation of the finer bile ducts, the necrosis of the biliary epithelium and the marked infiltration and perilobular and intralobular fibrosis correspond with the changes of infectious cirrhosis described by Mallory in 1911 and 1932 and by McMahon in 1931. The changes are similar to the clinical and pathologic disorder described by Hanot in his thesis published in Paris in 1875.

DEMONSTRATION OF MICRO-ORGANISMS IN EPIDEMIC ENCEPHALITIS (ST. LOUIS EPIDEMIC). ARTHUR WEIL.

Through the cooperation of the department of pathology of Washington University, St. Louis, I was able to study representative blocks of tissue from the brains of eight persons who died from encephalitis in the recent epidemic. In sections of each brain treated with paraffin and stained with cresyl violet or methylthionine chloride, U. S. P. (methylene blue), diplococci were demonstrated. They were from 0.6 to 1 micron in diameter, isolated or accumulated in small colonies or arranged in short or in long chains. The diplococci within the subarachnoidal spaces were somewhat larger than those in the brain tissue. They were not demonstrated, however, within the perivascular cellular exudate or within the foci of proliferated glia. These facts, together with the absence of an inflammatory reaction in the regions where these diplococci were found, suggest that they were able to multiply only after the defense reaction of the body had broken down, and that the process was either agonal or postmortem. The diplococci were not found as the result of accidental contamination, but must have been present at the moment of death, because they were found in the centers of blocks of tissue fixed with formaldehyde as well as in the peripheral portions.

These observations are reported because the simultaneous appearance of one and the same type of micro-organism in colonies and chains in each of a number of brains received from different hospitals is unusual. Furthermore I was impressed by the large number of "hyperkinetic" types of encephalitis among the cases occurring in St. Louis. Von Economo has advanced the theory that perhaps in this type there is a mixed infection as compared with the classic ophthalmoplegic-lethargic type, which he considered a pure virus infection.

DISCUSSION

E. F. HIRSCH: Were there leukocytic exudates or reactive changes in the tissue about the foci of bacteria?

N. PAUL HUDSON: It is not generally agreed what the etiology of the epidemic encephalitis of von Economo is. Numerous investigators believe that it is as yet unknown, and bacteria are not commonly accepted as the primary cause. The significance of the diplococci, as shown by Dr. Weil, is uncertain owing to the failure of other workers accurately to reproduce the disease with them. There is a difference of opinion as to the actual nature of the epidemic that occurred in St. Louis, whether it was of the von Economo or of a different type.

If one looks into the preliminary reports (Muckenfuss) of the attempts to isolate an infectious agent from the cases occurring in St. Louis, one finds that bacteria that could be considered significant have not been recovered. On the other hand it appears that injection of material from human brains into monkeys and mice has transmitted an infectious agent that is not cultivable on bacteriologic mediums, is not visible, is filtrable, and, hence, falls in the general group of viruses.

Under these circumstances, the primary significance of the diplococci in the brain is doubtful. They were apparently present before or at death, and I should like to ask Dr. Weil what the intervals of time and the conditions were between death and the fixation of tissue.

L. E. DAY: Epidemics of encephalitis have occurred in horses, and from the brain tissues of these animals many different kinds of bacteria have been cultured, but none has proved to be the infectious agent.

A. WEIL: The usual procedures for preserving and storing brain tissues were followed in the material I studied. It was furnished to me in blocks hardened in formaldehyde. My study was entirely morphologic.

MYOCARDIAC CHANGES IN HYPERTENSION. VICTOR LEVINE.

This article will appear in full in a later issue of the ARCHIVES.

NEW YORK PATHOLOGICAL SOCIETY

Regular Meeting, Oct. 26, 1933

PAUL KLEMPERER, *President, in the Chair*

AN INSTANCE OF PLASMOCYTOMA WITHIN A TUBERCULOUS CAVITY. DAVID PERLA.

A man, aged 68, stated that he had had a productive cough for the past fifteen years. In January, 1932, his cough became more severe and spasmodic, and the sputum was blood-streaked for several weeks. He had severe anorexia and slight loss of weight. At that time he showed signs of consolidation of the right apex, with marked dulness, bronchial breathing and crepitant râles. He had a slight fever for a few days, and the sputum was found to contain tubercle bacilli. Roentgenograms showed a large dense shadow in the right upper lobe. There were numerous nodular infiltrations throughout both lungs; these were interpreted as metastatic nodules in addition to tuberculosis. A mass was felt in the right lower quadrant of the abdomen, and roentgen examination suggested the presence of a malignant condition in the region of the cecum. The patient was fairly comfortable during the following eight months. Then dizzy spells, difficulty in walking and defects in speech and memory developed. In January, 1933, there developed spastic right hemiplegia and complete motor aphasia. He died one month after admission to the hospital.

Autopsy disclosed a primary carcinoma of the cecum with metastases to both lungs and to the brain and thyroid, and generalized arteriosclerosis with slight coronary sclerosis. There was evidence of chronic bilateral pulmonary tuberculosis. A large fleshy tumor was found in the right upper lobe, apparently situated within a tuberculous cavity. In the central portion of the tumor was a firm nodule 2 cm. in diameter composed of dense, yellowish tissue containing several areas of calcification and possibly osseous formation.

The tumor was composed of plasma cells throughout. The other nodules in the lung were definitely adenocarcinomatous metastases from the cecal carcinoma. Of interest is the occurrence of this unusual plasmocytoma within a tuberculous cavity in a patient who had a primary carcinoma of the cecum with metastases to the lungs.

DISCUSSION

ALFRED PLAUT: Have the bones been irradiated with the roentgen rays in this case?

DAVID PERLA: No, we did not get permission for a complete autopsy. Has any one seen a case like this of a plasma cell tumor in the lung? I have tried to find one.

A CASE OF COOLEY'S ANEMIA. DAVID PERLA.

A boy, aged 9 years, with a previous history of measles at 5 and tonsillectomy at 6 years of age, was admitted to the hospital with weakness, edema of the lower extremities and progressive anemia. Three years prior to admission a large spleen had been noted. Shortly thereafter edema of the legs was observed, but this cleared up spontaneously in two months. The patient was said to have been anemic practically since infancy. In addition to marked pallor, he presented a subicteric tint of the skin, the mongolian facies and the rachitic rosary. There was prominence of the frontal and parietal bones. There was a sanguinopurulent discharge from the left ear. The heart was enlarged to the left. A precordial systolic murmur was heard. The spleen and liver were markedly enlarged.

The hemoglobin was 30 per cent; the red blood cell count, 2,200,000; the white blood cell count, 10,500, with a differential smear showing 2 per cent myeloblasts and 3 per cent myelocytes. Normoblasts and megaloblasts were present. Erythroblasts were seen in small numbers. There were marked poikilocytosis and anisocytosis.

A roentgenogram of the skull showed marked thickening of all the bones, with thinning of the cortex and a granular medulla. All the long bones showed thin cortices.

A diagnosis of Cooley's anemia was made.

The patient had a continuous fever up to 103 F. In spite of extensive liver, gastric and iron therapy with numerous transfusions, the anemia could not be improved, the red cell count remaining around 2,000,000. During the rises in temperature there was no evidence of any hemoclastic crisis, the urine showing no evidence of hemoglobin.

About one year after his first admission, following a transfusion, the patient died with the symptoms of dyspnea and cyanosis.

At autopsy a severe anemia was evident. The liver weighed 1,420 Gm., and the spleen, 725 Gm. There was a marked hemosiderosis of the mesenteric and retroperitoneal lymph nodes, with hyperplasia of the hemolymph glands and osteoporosis of the bones. The calvarium was thickened and measured 9 mm. in the occipital and frontal regions. The increase in thickness was due to a thickened medulla which was traversed by numerous fine trabeculations. The inner and outer plates each measured less than 1 mm. The vertebral medulla was chocolate brown.

Microscopic sections of the liver, pancreas, kidneys, mucosa of the stomach, and lymph nodes gave positive reactions for iron. Periportal accumulations of lymphocytes and plasma cells were seen. The spleen showed a moderate hyper-

plasia of reticulum cells; the sinusoids were congested; the endothelial elements were prominent and contained a brownish pigment that did not stain for iron. The malpighian follicles were atrophic. Scattered throughout the spleen were numerous eosinophilic myelocytes. The bone marrow was highly cellular, showing primarily myelocytes, erythroblastic elements and many groups of foam cells. Many of these contained ingested red cells.

DISCUSSION

PAUL KLEMPERER: Of what race was the child?

DAVID PERLA: Italian. The picture you see in the bone marrow is present in sickle cell anemia and in congenital hemolytic icterus, but these three congenital anemias leading to rapid hyperplasia of the bone marrow are the only diseases which produce that picture.

PAUL KLEMPERER: I have seen the same large foam cells in the spleen in Cooley's anemia.

DAVID PERLA: They did not give the usual lipoid stain of the foam cells.

HYPERTROPHY OF THE HEART DUE TO STORAGE OF GLYCOGEN. W. ANTOPOL, J. HEILBRUNN and L. R. TUCHMAN.

A case of van Gierke's disease is reported which is believed to be the first one in which necropsy was done to be recorded in the American literature. There was tremendous enlargement of the heart together with hepatonephromegaly in a boy aged 4½ months. The heart weighed 85 Gm. Microscopically there was a massive infiltration of the myocardial fibers with glycogen. The liver and kidneys were the site of a similar deposition. The presence of appreciable amounts of galactogen was ruled out by comparison of Best's carmine preparations with those stained by iodine. Chemical analysis of tissue placed in alcohol after one month's fixation in formaldehyde showed 3.57 per cent glycogen in the heart, 3.25 per cent in the liver and 4.34 per cent in the kidney (wet weight). A relationship to idiopathic hypertrophy of the heart and rhabdomyoma of the heart is suggested.

DISCUSSION

DAVID PERLA: Is the hypertrophy of the heart due to the mechanical storage within these cells, or did you see actual hypertrophy of the nuclear elements?

LOUISE W. RAUH (by invitation): About one and a half years ago an Italian boy, aged 20 months, was seen at Mount Sinai Hospital. He was thought to have a disturbance in glycogen metabolism. He had been perfectly well until 8 months of age. At that time it was noticed that his abdomen seemed to be larger than normal, and for the next year it increased in size. The birth and development had been normal, and the family history was irrelevant.

The child was pale, but fairly well nourished; he was somewhat stunted in growth. He was mentally normal and alert. There was an odor of acetone to his breath. The abdomen was large, the liver extending to below the umbilicus. The spleen could not be felt. There was no ascites. The remainder of the examination revealed no abnormalities.

On many occasions the urine showed acetone. There was a great increase in amylase, 19 units in a twenty-four hour specimen by the Elman method. There was no free glycogen, and no glycosuria after ingestion of 40 Gm. of dextrose.

The blood showed amylase 0.9 unit by the Elman method, from 2 to 6 units being normal. There was no free glycogen. The sugar content during periods of fasting varied between 40 and 65 mg. The curves for sugar tolerance were biphasic and showed prolonged elevation. There was a normal response of the blood sugar to epinephrine and to insulin. The urea was 17 mg., and the total cholesterol, 310, 415 and 395 mg. with an ester of 185, 120 and 290 mg. respectively. The lecithin was 325 mg.; the total fat, 2,300 mg. The calcium and phosphorus were normal. The icteric index was 6; the van den Bergh direct and indirect

tests were negative. The tests for hepatic function showed galactose and bromsulphalein to be normal. The tuberculin and Wassermann tests were negative. The cutaneous test for Echinococcus was negative. The blood count was normal; the Best stain of the blood smears showed no deposit of glycogen in the leukocytes.

Epinephrine therapy was attempted with subcutaneous injection of 0.2 cc. of a 1:1,000 solution twice a day for eight days. Following this there was no increase in the blood sugar during fasting nor any decrease in the size of the liver. Thyroid therapy was tried in an attempt to liberate the glycogen. It was begun with small doses, later increased to 0.12 Gm., administered three times daily, but after two weeks, because of loss in weight, it was discontinued. There was no change in the level of blood sugar during fasting or in the size of the liver.

The patient stayed in the hospital for three months, and grew 3 cm. in height and gained 1,800 Gm. The circumference of the abdomen increased 4 cm. At no time, in spite of the low blood sugar during fasting, were there any hypoglycemic reactions.

The patient is being followed; he is growing somewhat, but the size of the liver is steadily increasing.

PAUL KLEMPERER: Would it be impossible after four weeks to try to determine the presence or absence of enzymes in the organs?

CARL ZELSON: Dr. Schönheimer's conclusion that this was due to a disturbance in glycogen metabolism was based on the fact that in this condition after seven days the liver contained tremendous amounts of glycogen; in other words, in the normal liver glycogen is immediately broken down, and in this condition glycogen is not broken down in the liver. This is the main point in the interpretation of the disease. There is a disturbance in the glycolytic power within the cells of the liver.

LESTER R. TUCHMAN: The material was fixed in formaldehyde; therefore no studies of enzymes could be made. In spite of the fact that our figures are so high, large amounts of glycogen had undoubtedly been lost owing to the method of fixation. In one of the cases reported, half of the dry weight of the liver was glycogen, and in another case about 40 per cent of the dry weight was glycogen, so that apparently it can be stored in tremendous amounts. The clinical symptoms which Dr. Rauh described occurred in about half of the reported cases. The only common finding was the acetonuria. One of the patients had blood sugar as low as 15 mg. per hundred cubic centimeters without any hypoglycemic symptoms. One case is reported with no sugar in the blood ante mortem. Some patients were sensitive to insulin and some were not. Dr. Rauh's patient responded to epinephrine with a hyperglycemia; most did not. They all showed blood sugar that was low or "low normal." Kimmelstiel's patient with deposits of glycogen in the brain showed definite cerebral symptoms.

W. A. ANTOPOL: In answer to Dr. Perla's question, the nuclei are normal in size. If the fibers were reconstructed to aggregate solid units, they would probably approximate the normal dimensions. The storage of glycogen per se within the "hollowed-out" fibers caused the tremendous increase in size.

This condition is thought to be due to the persistence of the fetal type of glycogen metabolism in which the glycogen is mobilized with difficulty. Needham has shown the glycogen to be in a stable form just prior to birth. Diamanopoulos found further that more epinephrine is needed to mobilize glycogen in the new-born.

HODGKIN'S DISEASE IN THE LUNG. SYLVAN E. MOOLTEN.

The fundamental nature of Hodgkin's disease is still a problem; in respect to this problem the parenchyma of the lung, because of its unique construction, is a sort of arena in which can be observed the unfolding of the morphogenic characteristics of the disease in probably their simplest form. Most significant in this respect are the type and arrangement of the interstitial tissue, the epithelial content and behavior, and the air spaces themselves. The comparison of Hodgkin's

disease in the lung with certain infective granulomas of known etiology (e. g., tuberculosis and actinomycosis) on the one hand, and with tumors (including lymphosarcoma) on the other, tends to fortify the standpoint that Hodgkin's disease is primarily an inflammatory reaction of granulomatous character.

The material is drawn from a detailed study of eight cases embodying various aspects of the pulmonary lesion. In general two phases of the disease could be distinguished, the proliferative and the exudative. These were usually present simultaneously within the same area and even within the same lesion, the proportion of proliferative response to exudative response varying in individual cases. In general the proliferative type of lesion tended to display its most characteristic development within the interstitial structures of the lung, i. e., the walls and connective tissue sheaths of the bronchi and blood vessels, the interlobular septums and, above all, the interalveolar septums (i. e., the walls of the alveoli). The exudative phase occurred not only in these situations (where it was recognized with ease in some cases and with difficulty in others) but particularly within the air spaces of the alveoli. In no other tissue of the body is it possible to distinguish with such clarity the various degrees and kinds of the exudative response.

On the basis of personal observations of Hodgkin's disease as it implicates the lung together with findings reported in the literature certain conclusions are drawn. Hodgkin's disease is primarily an inflammatory condition, considered not only from the standpoint of its evolution within the organism as a whole but in particular from the standpoint of the type of response elicited within the lung.

What may be called the "pure lesion" as seen growing within the lumen of the alveolus unencumbered by any sort of stroma or other preexisting tissue is revealed not as the product of a specific proliferation of cells but rather as a specific mixture of cells (cells of histiocytic type, fibroblasts, cells imigrated from the blood).

Highly resistant structures such as the thick-walled arteries may become invaded by the surrounding infiltration, and on the other hand delicate structures such as the walls of the alveoli may likewise be infiltrated; in either case the result is not compression or destruction, but uniform infiltration with preservation of the underlying framework. This speaks for permeation by a virus or soluble toxin rather than for direct invasion by cells themselves as in a tumor. The proliferation of cells resulting in the specific mixture of cells is then primarily derived from the differentiation of the reacting preexisting autochthonous mesenchymal elements in response to the stimulus in loco.

On a similar basis it is possible to account for the abundant nonspecific inflammatory lesions. These consist of the mild "catarrhal" reaction of the alveoli, the more marked fibrinous exudative reaction and their subsequent end-stages. The catarrhal stage ends in the degeneration of the desquamated alveolar epithelial cells with liberation of their cholesterol in the form of the characteristic boat-shaped crystals. The fibrinous stage ends in some form of organization ("carnification") either by ordinary fibroblasts or by varying proportions of fibroblasts and cells specific to the granulomatous lesions ("pneumonia granulomatosa"). The ultimate fate of such lesions is transformation into ordinary scar tissue.

The alveolar epithelium does not play a mere passive part in the lesions but is apparently actively stimulated. In the exudative stage it undergoes rapid proliferation and desquamation in the form of large numbers of mononuclear or multinuclear phagocytic cells similar to those seen in many portions of tuberculous or actinomycotic lesions in the lung. These cells bear no more than a superficial resemblance to the Langhans giant cells or the Sternberg-Reed giant cells and are never seen to participate in the formation of the granuloma. In the proliferative and healing stages these cells form a continuous row of cuboid epithelium lining the infiltrated alveolar septums, often giving rise to the appearance of glands.

The distribution of the lesions within the lung conforms to that found in many bacterial infections of the lung. The proliferative phase occurs in two forms, peribronchial and pleurogenous, analogous to the two forms of interstitial pneumonia, peribronchial and pleurogenous (e. g., complicating grip or measles as an acute infection due to Streptococcus haemolyticus, or as part of tuberculosis or actinomy-

cosis). The exudative phase produces, in addition, a form of gelatinous lobar or lobular pneumonia.

From a synthesis of these findings the following classification of Hodgkin's disease of the lung is compiled: (1) granulomatous panbronchitis and bronchopneumonia, (2) exudative lobar and lobular pneumonia (gelatinous pneumonia, organizing pneumonia), (3) miliary, submiliary and multiple isolated nodular lesions (hematogenous, lymphogenous) and (4) granulomatous pleurogenous pneumonia (the primary form is rare, one case being reported; the secondary form is frequent, and is due to direct invasion of the pleura from the adjoining infiltrated mediastinum).

DISCUSSION

FRED W. STEWART: I think that this is a splendid contribution, and I watched Dr. Moolten's photographs with a great deal of interest because I have seen all these changes myself, and have come to much the same conclusion regarding their pathogenesis. I am glad to find some one who is willing to uphold the infectious nature of Hodgkin's disease despite all the recent negative bacteriologic findings by Twort and others, and especially after the suggestions in the last section of the Rose research on lymphadenoma, which tend to discourage the idea of Hodgkin's disease being an infectious granuloma. There is one type of involvement of the lung in Hodgkin's disease I should like to ask about. Within the last month or six weeks I saw a patient with typical Hodgkin's disease. He eventually died, showing essentially no lesions. He had a specific process in the spleen, but the manner of death was very unusual. A very intense interstitial emphysema suddenly developed, and at autopsy we found the usual signs of emphysema, an intense mediastinal emphysema, with spread of air to the tissues of the thoracic wall and neck. The lungs were tremendously distended. There was no point of perforation, and the only possible assumption was a rupture of the pulmonary alveoli. In the bronchi we found a complete cast of the bronchial tree, much as one finds in bronchial asthma. There was no history of previous attacks of bronchial asthma. The exudate in the bronchi was thick, of nearly the consistence of agar. There were a great many plasma cells and eosinophils, but nothing of the characteristic structure of Hodgkin's disease. On section the exudate in the bronchi, this heavy, thick mucinous cast, was full of eosinophils. That might have agreed well with bronchial asthma, but in the centers of most of these thick mucinous cores were areas of typical caseation. They had undergone caseous necrosis. In view of that, and of the fact that the patient had Hodgkin's disease and had never mentioned having had bronchial asthma I thought that this would have to be classed as one of the peculiar manifestations of Hodgkin's disease. Has Dr. Moolten ever seen anything like this?

SYLVAN E. MOOLTEN: In regard to the interesting type of bronchitis described by Dr. Stewart, the literature contains references to somewhat similar findings. I have not seen quite the same thing in the series I have studied, but in Hodgkin's disease lesions involving the bronchi have been known for many years and are well described in Ziegler's monograph of 1911. The gross appearance is often that of an ordinary catarrhal bronchitis, or it may be more like that of tuberculous bronchitis. Frequently there are stricture and stenosis of the bronchus and sometimes complete occlusion with atelectasis and secondary bronchiectasis. Bronchoscopy should prove useful in certain cases in which material is needed for biopsy in making a diagnosis. Characteristic findings by which one may suspect the diagnosis on gross inspection include the presence of certain areas of opacity or plaque formation in the mucous membrane, which are not quite the same as those seen in certain cases of carcinoma. At their periphery they tend to fade indefinitely into the surrounding mucosa. Furthermore, the lesions are usually distributed bilaterally and in a disseminated manner rather than grouped as a single lesion as in carcinoma. The presence of fibrinous exudate within the bronchi I should interpret as expressive of the more intense exudative reaction of the disease.

The question arises whether these acute exudative reactions, the fibrinous or catarrhal reactions, are specific or nonspecific. Morphologically they are unquestionably nonspecific. The question really concerns their specific or nonspecific causation, and that is an important point possibly admitting a certain amount of controversy. My own belief is that they are of specific causation, based on the findings in the lung itself. The distribution of such lesions does not correspond to the distribution of a bronchogenic lesion and does not follow the pathways of a bronchogenic dissemination such as might be produced by aspiration of infective material containing bacteria from the bronchi. The process suggests rather a diffusion of the virus itself from the central bronchial focus into the surrounding periphery in the parenchyma. The possibility that bacteria may secondarily contaminate the lesions in the lung has been mentioned by others and, incidentally, has been given as one of the reasons for the necroses often seen in these lesions. Actually, however, bacteria are rarely seen.

There are other points which would also speak for the diffusion of the hypothetic specific virus itself into these areas as a cause of the exudative reaction, such as the gradual transition from the nonspecific organizing pneumonia into the definitely specific lesions, in which one can see the gradual increase in the proportion of the specific cells over the nonspecific fibroblasts, forming a lesion in all respects identical with the first, except in the varying amount of the specific types of cells present.

The necrosis of the exudate in the bronchi mentioned by Dr. Stewart might speak for secondary infection. I have seen similar necrosis within alveolar exudate composed of masses of fibrin, with some leukocytes and alveolar phagocytes; the appearance at times is closely similar to the early lesion of tuberculosis. I do not know how to explain it. I do not know whether it is possible to explain it on the basis of the action of the specific virus itself causing necrosis of the exudate or of incidental bacterial contaminants. The stains I have made of such necrotic exudate have shown no organisms—neither ordinary bacteria nor tubercle bacilli.

AMYLOIDOSIS OF THE BONE MARROW, WITH REPORT OF A CASE. I. E. GERBER.

Amyloidosis of the bone marrow is a rare lesion. A number of instances of involvement of the media of small vessels of the bone marrow have been described. In addition a number of cases of primary amyloid tumors of the bone marrow have been reported. These cases are characterized by massive local accumulation of amyloid in one or several bones, with or without infiltrations in other organs. A third type is that of amyloid deposits in a true blastoma of the bone marrow. The multiple myelomas are the blastomas most frequently involved. No cases of diffuse involvement of the bone marrow have been reported hitherto.

The case reported is that of a white man, aged 44, who complained of generalized weakness and muscular pain. On examination hepatomegaly, signs of nephrosis and hyperchloesteremia were found. Two years later hypertension, renal insufficiency and a collapse of the ninth dorsal and first lumbar vertebrae developed; the latter was thought to be the result of lipoid infiltration of the bones. Postmortem examination revealed generalized amyloidosis with diffuse amyloid infiltration of the bone marrow. No cause for the amyloidosis was found.

The amyloid in the organs stained with congo red and with the aniline dyes, but not with iodine. In the bone marrow the amyloid exhibited even more marked variations in staining and reacted only with the aniline dyes. There was marked destruction of the spongy bone without any tendency to the formation of new bone. Careful search failed to reveal any evidences of underlying disease of the bone marrow; no blastoma was found. As there was no tumor-like accumulation of the amyloid or underlying blastoma, this case represents a distinct type of amyloid disease of the bone marrow, i. e., diffuse amyloidosis of the bone marrow.

DISCUSSION

DAVID PERLA: I have seen four instances of so-called primary amyloid disease in which no apparent etiologic factor could be found. The case presented is different from those which I have seen in that the bone marrow was not involved in any of them.

I think "typical amyloid disease" would be a better term than "primary amyloid disease," because one does not know what the nature of the amyloid deposition is, particularly if there is no destructive process in the body. In the instances which I have seen, the liver and spleen were not involved, and Lubarsch has stated that in atypical amyloid disease the amyloid was either slight or absent in the usual sites, and appeared in unusual sites. I have never seen a case like the one reported by Dr. Gerber, and I am very glad to have heard his presentation.

I. E. GERBER: I want to say a few words about the term "atypical." It was first employed by Lubarsch to denote an unusual localization of amyloid, in which the spleen and the liver, as Dr. Perla mentioned, are not involved. In going over the literature on amyloidosis, I have come across many instances in which there have been atypical localizations of amyloid, and in which the spleen and liver were involved, and these cases likewise showed all the other characteristics of amyloidosis, some of which were atypical, the staining reactions to the usual amyoid stains, for example, and the nodular deposits of amyloid. All of these may be found in cases of generalized amyloidosis—hence one must be careful in the use of the term "atypical." One must recognize the fact that some cases do tend to show atypical reactions, they do tend to spare the spleen and the liver, but they are in no way different from those of generalized amyloidosis. I do not want to enter into any new classification of the disease; the characteristics of an atypical amyloidosis are so typically found in generalized amyloidosis that I do not think it would be well to put in a third classification, unless there is a good reason for doing so.

A CASE OF CARCINOMA OF THE STOMACH TREATED AS PERNICIOUS ANEMIA: DURATION, OVER SIX YEARS. ANGELO M. SALA.

A woman, aged 65, was first seen in April, 1927, when she complained of weakness, poor appetite and a recent gradual loss of weight with increasing pallor of the skin. Her blood picture was as follows: erythrocytes, 1,500,000; hemoglobin, 40 per cent by the Dare method; color index, 1.3; leukocytes, 4,300; polymorphonuclear neutrophils, 50 per cent; lymphocytes, 46 per cent; large mononuclears, 3 per cent; eosinophils, 1 per cent. The coagulation and bleeding times were within the normal range. The stained smear showed poikilocytosis, anisocytosis, polychromatophilia and macrocytosis. There were occasional megaloblasts; normoblasts were not encountered. A reticulocyte count showed complete absence of reticulocytes in a count of several thousand erythrocytes. The report to the attending physician was that the blood picture strongly suggested addisonian anemia, but other diagnostic procedures were necessary to substantiate or exclude this diagnosis. The patient was given liver and hydrochloric acid with such marked improvement in two weeks that the physician was satisfied he was dealing with pernicious anemia, and continued to treat the patient accordingly. Her body weight, general clinical condition and hemoglobin were satisfactory during this time; on May 10, 1932, she weighed 143 pounds (65.86 Kg.), and her hemoglobin was 75 per cent. In August, the patient discovered a "lump" in her epigastrium. Surmising that her physician would recommend an operation, for which she considered herself a poor risk, she did not consult him until her regularly scheduled appointment in November. At this time a freely movable tumor the size of an orange was felt to the left of and above the umbilicus. There was no vomiting, but appetite had begun to fail. She was then sent to me, at the clinic of the New York City Cancer Institute, where the clinical diagnosis of carcinoma of the stomach was confirmed by the roentgenologist. At that time the hemoglobin was 35 per cent by the Dare method, and the red cell count was 1,000,000. The

morphology of the blood was about the same as in 1927; reticulocytes were absent. Operation and roentgen ray treatments were refused, and the patient gradually weakened and died at home on Aug. 5, 1933.

A postmortem examination limited to the abdomen revealed a bulky carcinoma of the stomach involving the distal two-thirds and the pyloric region. The tumor was necrotic, and there were metastases to the perigastric nodes and to the liver. There was no ascites. Histologically, the tumor was an adenocarcinoma, grade 2.

The question presents itself: Was this a case of gastric carcinoma arising in a patient with addisonian anemia, or did the patient have cancer of the stomach all along? I believe the latter has been the case; I have never seen gastric cancer develop in a patient with true pernicious anemia, and the duration is by no means against this probability. On the other hand, the case well illustrates the difficulty often encountered in basing a differential diagnosis between pernicious anemia and the anemia of gastric carcinoma on the examination of the blood alone. Pepper and Farley say in their "Practical Hematological Diagnosis": "Among the conditions which produce an anemia most closely simulating Addisonian anemia is carcinoma of the stomach or of the ascending colon. When such an anemia precedes local symptoms the diagnosis may be very much in doubt." It is my belief that the diagnosis of pernicious anemia is to be made largely by exclusion, and that it should remain provisional until all diagnostic procedures, of which examination of the blood is only one—and not necessarily the most important—are exhausted. Even in cases of apparently true primary anemia, in which the favorable response to the therapeutic test imparts a feeling of security, the possibility of a malignant condition of the gastro-intestinal tract and the desirability of roentgen studies of the digestive tract at not too long intervals need not be forgotten.

DISCUSSION

ALFRED PLAUT: I cannot say anything in relation to the pernicious anemia, but as far as the duration of the disease is concerned, it would not be as unusual as most people believe to have a carcinoma of the stomach with a course of six years or more. When gastro-enterologists go over the records of patients whom they have followed for years, they often find cases in which a long history of gastric disturbance ended with an operation for carcinoma or with an autopsy revealing this condition, so that in these cases one wonders whether the disease did not start long before the diagnosis was made or whether the patients had another condition of the stomach, and carcinoma developed later on. I have seen patients seeking treatment for from twelve to fifteen years concerning whom, incredible as it may seem, the most logical conclusion is that they probably had the same disease all the time. I remember one patient at the Memorial Hospital who, eight years after a biopsy which positively showed carcinoma, was still in the same condition, and the files of the Memorial Hospital contain records of cases which have been under observation longer than that.

ANGELO M. SALA: I entirely agree with Dr. Plaut. I believe that the patient had a carcinoma of the stomach from the beginning, and I present the case not because of its duration, but to call attention to a mistake that could and should have been avoided.

Book Reviews

The Science of Radiology. Authorized by the American Congress of Radiology. By twenty-six contributors. Edited by Otto Glasser, of the Cleveland Clinic Foundation. Price, $4.50. Pp. 450, with 108 illustrations. Springfield, Ill.: Charles C. Thomas, Publisher, 1933.

One of the projects of the executive council of the recent American Congress of Radiology was the publication of a book which would record the outstanding developments in radiology from the time of Roentgen's discovery to the time of the congress. Beginning with the story of Roentgen and of Pierre and Marie Curie by Otto Glasser and an account of American pioneers in radiology by William A. Evans, there follows a consideration of roentgen physics, apparatus and tubes and recording mediums and screens. Dosimetry is discussed. Percy Brown summarizes in fifty pages the progress in roentgen diagnosis to date. Military roentgenology, roentgen cinematography and roentgen therapy are adequately described. Radium physics and dosimetry are considered by Failla and Quimby, while radium therapy is handled by Bowing and Fricke. George M. MacKee writes a valuable chapter on cutaneous roentgen and radium therapy. There are also chapters on protection, teaching, radiologic societies and literature, the nature of the cosmic rays and the Gurwitsch rays, and the foundations of therapy with ultraviolet, visible and infra-red radiations.

Chapters XVII and XVIII are of special interest to pathologists. Hermann U. Muller, professor of biology in the University of Texas, undertakes the consideration of the effects of roentgen rays on the hereditary material. Gene mutations and chromosome changes are produced by roentgen rays in germ cells of all types: in spermatozoa (whether irradiated while in the testis or after they have been received by the female), spermatogonia, mature eggs, oocytes and oogonia. They can also be produced in somatic cells. However, all cells are not equally susceptible. Cells under anesthesia are more susceptible than nonanesthetized cells, but cells in a state of undernutrition are less susceptible. Heat or cold accompanying irradiation has little or no effect. These statements are based on studies on Drosophila, wasps and other insects as well as on mice and on various plants, including barley, tobacco, jimson weed, maize, wheat, cotton, primroses and snapdragons. Similar effects have been found when using radium. As a practical conclusion, it is important for human beings to avoid the possibility of having mutations produced in their germ cells by irradiation. It is to be expected that, because of their recessiveness, such mutations would ordinarily fail to manifest themselves until several generations after they had been produced, causing physiologic disturbances and elusive effects that lowered the general vitality or efficiency more often than conspicuous morphologic abnormalities, which are difficult to recognize and deal with. Of course, such effects could be produced if the reproductive organs received the radiation, and if reproduction occurred subsequently to this, as when the radiation is used for purposes of temporary sterilization. These conclusions rest on the plausible premise that the hereditary material of man is affected by irradiation in a similar way to that of insects and plants.

Charles Packard, of the institute of cancer research, Columbia University, devotes a short chapter to a summary of the biologic effects of roentgen rays and radium. When roentgen and gamma radiations are absorbed in living tissues they initiate a series of changes which lead to temporary injury to the cells or to their ultimate death. The first step in the series is purely physical; the quanta of radiation collide with electrons of the atoms composing protoplasm and displace them from their normal positions in the system, or else remove them altogether. These changes lead to the breaking down of protein substances into simpler compounds which are, in a sense, foreign to the cells, with resulting alteration in the morphologic and physiologic condition of the cells. The latent period between

the moment of exposure and the appearance of a definite reaction depends on the dose and also on the kind of change which is chosen as an evidence of injury. The primary biologic effects of radiation are changes in the hydrogen ion concentration of protoplasm, in the permeability of the cell membrane, in viscosity and in the respiratory rate. The morphologic effects which accompany them are undoubtedly secondary. Cells are most sensitive to radiation during mitosis. It is a common observation that some cells which have received less than the lethal dose may recover perfectly and continue to grow and divide; the susceptibility of such cells is in inverse proportion to their recuperative powers.

The idea did not occur to the earlier investigators that radiation might promote the physiologic activities and growth of cells and tissues. There can be no doubt that some physiologic processes are quickened by roentgen and gamma irradiations, but there is no direct evidence that weak radiations are able to cause stimulation. Stephan contends that although growth is not accelerated, there are certain functional activities which are directly promoted by small doses of radiation, such as shortening of the coagulation time of the blood and increased diuresis. But in view of of the fact that increased cell division following irradiation has never been proved, it seems probable that other explanations for these phenomena must be found.

Whether cells recover or die after irradiation depends not only on the number of roentgens which they receive but also on the intensity of the beam. As with any injurious agent, as soon as the cells suffer damage they begin the process of repair; if the injury is inflicted slowly, as by a beam of low intensity, the cells are more likely to recover. With high intensities of radiation, the tolerance dose is only slightly higher than the erythema dose, whereas with low intensities it is much greater.

Long experience has shown that hard rays are more selective in their action than soft rays, but this difference in action is not due to the quality of the beams so much as to their intensity. Within the last few years the weight of evidence shows that all wavelengths are equally effective. There are many who do not agree that this statement can be applied to the erythema reaction. It is a matter of common experience that the skin will tolerate a larger dose of hard rays than of soft rays.

The book is a valuable compilation of the latest views on many phases of radiology. It is to be hoped that later editions of the work will fill the gaps left by the various contributors, and supply complete annals of the science of radiology.

Text-Book of Pathology. By Robert Muir, M.A., M.D., Sc.D., L.L.D., F.R.S., Professor of Pathology, University of Glasgow; Pathologist to the Western Infirmary, Glasgow. Third Edition. Price, $10. Pp. 957, with 546 illustrations. Baltimore: William Wood & Company, 1933.

The second edition of this textbook was reviewed favorably in the ARCHIVES (**12**:685 [Oct.] 1931). In the present edition the author has "endeavored to incorporate as far as possible the many and important advances made in Pathology since the previous edition was published." The number of pages has been increased from 872 to 957, and the number of illustrations from 501 to 546, but the price has been reduced from $14 to $10. There is no occasion for any further review at this time. The book is essentially an acceptable and useful text on the structural changes in human disease.

Books Received

TUBERCULOUS INFECTION IN MILK. A REPORT BY THE DEPARTMENT OF HEALTH FOR SCOTLAND. Special Report Series, No. 189. Price, 9d. Pp. 38. London: His Majesty's Stationery Office, 1933.

TEXT-BOOK OF PATHOLOGY. Robert Muir, M.A., M.D., Sc.D., LL.D., F.R.S., Professor of Pathology, University of Glasgow; Pathologist to the Western Infirmary, Glasgow. Third edition. Price, $10. Pp. 957, with illustrations. Baltimore: William Wood & Company, 1933.

REPORTS OF THE COMMITTEE UPON THE PHYSIOLOGY OF VISION: XIII. DETERMINATION OF THE SENSITIVENESS OF THE EYE TO DIFFERENCES IN THE SATURATION OF COLOURS. L. C. Martin, F. L. Warburton and W. J. Morgan. Medical Research Council, Special Report Series 188. Price, 1s., net. Pp. 42. London: His Majesty's Stationery Office, 1933.

THE MODERN TREATMENT OF SYPHILIS. Joseph Earle Moore, M.D., Associate in Medicine, the Johns Hopkins University; Physician in Charge, Syphilis Division of the Medical Clinic, and Assistant Visiting Physician, the Johns Hopkins Hospital, Baltimore. Price, $5. Pp. 535. Springfield, Ill.: Charles C. Thomas, Publisher, 1933.

LE POISON DES AMANITES MORTELLES. R. Dujarric de la Rivière. Price, 60 fr. Pp. 182, with 24 illustrations. Paris: Masson et Cie, 1933.

DE VENARUM OSTIOLIS, 1603, OF HIERONYMUS FABRICIUS OF AQUAPENDENTE (1533-1619). A facsimile edition of Fabricius' famous work on the valves of the veins, celebrating the quartrecentenary. With an introduction, translation, notes and reproductions of the original plates of the first edition (1633). Kenneth J. Franklin, D.M., Tutor and Lecturer in Physiology of Oriel College and University Demonstrator of Pharmacology, Oxford. Price, $3. Pp. 104, with 15 illustrations. Springfield, Ill.: Charles C. Thomas, Publisher, 1934.

L'INFECTION CHEZ LES INSECTES, IMMUNITÉ ET SYMBIOSE. A. Paillot, Docteur ès Sciences, Lauréat de l'Institut, Directeur de la Station de Zoologie agricole du Sub-Est. Pp. 535, with 275 figures. Trévoux: G. Patissier, 1933.

WILHELM CONRAD RÖNTGEN AND THE EARLY HISTORY OF THE ROENTGEN RAY. Otto Glasser, Ph.D., Director, Radiation Research Department, Cleveland Clinic. With a Chapter on Personal Reminiscences of W. C. Röntgen by Margaret Boveri (Berlin). Price, $6. Pp. 496, with 96 illustrations. Springfield, Ill.: Charles C. Thomas, Publisher, 1934.